Cost-effectiveness of controlling infectious diseases from a public health perspective

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Cover design: Pieter Troost/Studio Sanhaveld, Zeist
Cover photo (Aat getting his whooping cough booster vaccination): Pieter Troost/Studio Sanhaveld, Zeist
Lay-out: Theta Research, Zeist
Printed by: Ponsen & Looijen, Ede

ISBN 978-90-367-4645-8

The studies presented in this thesis were performed at the Centre for Infectious Disease Control (CIb), National Institute for Public Health and the Environment (RIVM), Bilthoven, the Netherlands.

RIJKSUNIVERSITEIT GRONINGEN

Cost-effectiveness of Controlling Infectious Diseases from a Public Health Perspective

Proefschrift

ter verkrijging van het doctoraat in de
Wiskunde en Natuurwetenschappen
aan de Rijksuniversiteit Groningen
op gezag van de
Rector Magnificus, dr. F. Zwarts,
in het openbaar te verdedigen op
vrijdag 4 februari 2011
om 14.45 uur

door

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geboren op 20 februari 1968
te Malmö, Zweden

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Kosteneffectiviteit van infectieziektebestrijding vanuit een volksgezondheidsperspectief

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Chapter 1

General introduction

HISTORICAL CONTEXT OF VACCINATION

The field of public health deals with preventive rather than curative aspects of health and with issues at the population level rather than the individual level. Public health has improved enormously since it became possible to control and prevent infectious diseases through vaccins and other pharmaceutical products.

The history of vaccination is closely connected to the control of smallpox (variola). Early records document efforts to prevent smallpox in China during the 17th century. Variolation – that is, deliberately infecting someone with (a mild case of) smallpox – was widespread in other parts of the world, notably in Constantinople. In 1721 Lady Montagu introduced the practice into England. Due to the procedure, however, 2-3% of those thus treated contracted and died from the dread disease (Plotkin & Plotkin 2009). The first scientific evidence of the connection between the less harmful disease cowpox (vaccinia) and the much deadlier variant smallpox was provided by the British farmer Benjamin Jesty. He deliberately inoculated his children with cowpox so they could attain immunity against smallpox. The local knowledge of this connection caught the attention of Edward Jenner (1749-1823), who developed a cowpox-based vaccine to protect humans and managed to produce vaccine in larger quantities. For this momentous achievement he is renowned as the inventor of vaccination (Plotkin & Plotkin 2009).

Debates on these attempts to prevent infection prompted questions about vaccinating the population. Daniel Bernoulli, born in 1700 in Groningen (the Netherlands), was the first scientist to calculate the gain in life expectancy by eliminating smallpox (Dietz & Heesterbeek 2000). In 1766 his work on smallpox was published. In it, he set forth two important epidemiological parameters: force of infection and case fatality rate. Interestingly, one of the standard functions used in economic utility theory, known as the Bernoulli utility function, was defined by the same Daniel (the Bernoulli family has produced many famous mathematicians) when he solved the St. Petersburg paradox.

Given the short history of controlling infectious diseases, developments during the 20th century have been particularly rapid. Most have been very successful too, saving millions of lives worldwide. Another important factor is the increasing affluence of the general population. This has contributed to the enormous gain in health and life expectancy during the last century, at least in developed countries. Without more and better food and improved hygienic circumstances, infectious diseases might not have been brought under control (Roberts 2006).

VACCINATION PROGRAMS

The most successful global vaccination campaign has been against smallpox, the first human infectious disease to be vaccinated against on a large scale. In 1979, about 100 years after the campaign began, a commission of eminent scientists announced that smallpox had been eradicated, and in 1980 it was endorsed by the World Health

Assembly of the World Health Organization (WHO website) The Dutch National Immunization Program started in 1957 with vaccination against polio, and today it includes vaccinations against 12 infectious diseases. Despite the famous words of Surgeon General William H. Stewart (in 1967), proclaiming that the fight against infectious diseases was over (Mooij 2007), it seems that the battle has not been won. The proportion of deaths attributed to infectious diseases declined rapidly in the Netherlands over the past 100 years (Figure 1.1). But this proportion has risen again, albeit slightly, over the past 60 years.

Intervention against a transmissible disease not only lowers the likelihood that an individual will become ill but it also reduces the exposure of the infection to others. Called herd immunity, this is a positive side-effect of vaccination on a large scale. Individuals with little or no protection against a certain disease are thereby indirectly protected, since the chance is slight that a susceptible individual will meet a contagious person. Therefore, decreasing the transmission of an infectious disease is one of the primary goals of public health vaccination programs.

Compliance with the Dutch National Immunization Program is high. Although the program has produced an overall high immunization level, the Netherlands has relatively large non-vaccinating clusters. They consist of individuals who are particularly vulnerable to infections that have more or less vanished from the rest of the Dutch population. Such groups persistently reject vaccination for religious

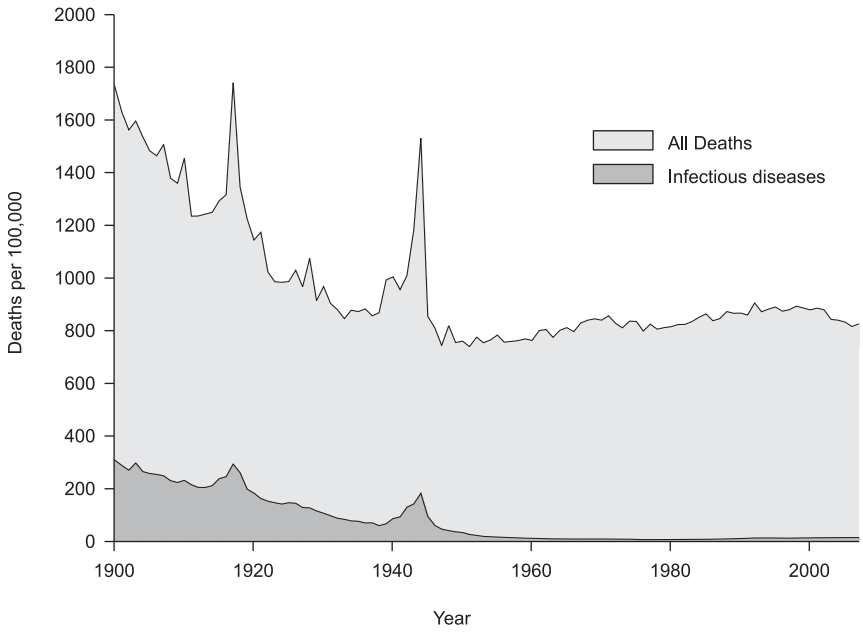

Figure 1.1 Deaths in the Netherlands per 100,000 inhabitants, due to all causes and to infectious diseases

Source: http://statline.cbs.nl/

reasons, among others. These pockets of unvaccinated individuals regularly suffer outbreaks of infections that have been nearly eliminated in the general population; one example is the recent outbreak of rubella (German measles) (Hahné et al. 2009). Besides these known clusters, every now and then vaccination is widely rejected, often on scientifically untenable grounds (André 2003).

Ideally, vaccinating small children would assure life-long immunity to infection, but in reality not all vaccines are equally efficacious. Vaccination-induced immunity against *Bordetella pertussis*, a bacteria causing pertussis (whooping cough), seems to wear off over time; that is, vaccinated individuals become susceptible to infection. Waning vaccine-induced immunity is a public health problem, as one aim of the program is to protect unvaccinated individuals and the desired herd immunity effect fails to occur.

PANDEMIC INFLUENZA

Influenza, one of the most common infectious diseases, causes large numbers of deaths worldwide. A seasonal influenza epidemic is expected annually. Even though infection provides immunity, new epidemics appear every year because the virus is continuously changing, a process called antigenic drift. These epidemics appear in the winter in the northern hemisphere, where between 5% and 25% of the population is infected each year (Jordan et al. 1958, Glezen 1996). They are caused by influenza viruses of type A, B, or C. There are several subtypes, denoted by their hemagglutinin (the "H" number) and neuraminidase (the "N" number).

Influenza pandemics are worldwide epidemics that occur when a new subtype starts circulating in the human population. A new virus is not necessarily more pathogenic or virulent than one causing a seasonal epidemic. Rather, the greater number of infected individuals expected during a pandemic is due to less pre-existing immunity among the population. The 20th century has seen three large influenza pandemics, which have taken a very high toll of human lives (Kilbourne 2006). All three were caused by influenza A viruses of different subtypes. As the Spanish flu (A/H1N1) moved in waves around the world in 1918-1919, it claimed at least 40 million lives. In 1957-1958 the Asian flu (A/H2N2) caused another pandemic. By then, antibiotics were available to treat bacterial co-infections, contributing to lower mortality than in earlier pandemics. Estimates put the death toll from this Asian flu at roughly two million. A third pandemic, the Hong Kong flu (A/H3N2) of 1968-1969, killed even fewer people, around one million. Experts have long been concerned about the timing and extent of a new influenza A pandemic. Their concerns became reality when the novel A/H1N1 virus caused a new pandemic in 2009. However, this pandemic turned out to be mild; the number of (registered) deaths according to the World Health Organization was around 18,000 worldwide (WHO website).

One virus with pandemic potential is A/H5N1, causing 'bird flu' or avian influenza. It is mainly transmitted to people in close contact with sick domestic birds

and has claimed a substantial number of human victims. To be prepared if such a virus were to gain human-to-human transmission capacity, many authorities started to stockpile antiviral drugs when these became available. Antiviral drugs make it possible to treat and prevent influenza by pharmaceutical means. These drugs are seen as a powerful resource to contain or even mitigate a pandemic in the absence of an effective vaccine (Longini et al. 2004, Ferguson et al. 2006). Even though the most recent pandemic was caused by an influenza A/H1N1 virus, the threat of a pandemic caused by an influenza A/H5N1 virus remains, and vaccines against the virus are continuously being developed and improved.

ECONOMIC EVALUATIONS OF INFECTIOUS DISEASES

Recent technological advances have generated a number of vaccines that have been of great importance to public health (André 2003, Kitchen & Vaughn 2007). This progress has enhanced the possibility to prevent and control epidemics, but the research and development costs of producing new vaccines have also increased. As these costs rise and the health effects at the population level decline – for instance, because the target group becomes smaller or the disease less prevalent – the relation between cost and effect becomes larger in the context of public health. The question arises whether intervention is worthwhile from a social and economic perspective. That is, are the costs that are incurred to prevent disease acceptable, given the amount of health gained? To answer this question, cost-effectiveness analyses are performed. These analyses entail estimating the cost per life year gained or another criterion of health improvement. The cost-effectiveness of public health interventions or programs has become a key element in the decision-making process (Houweling et al. 2010). Specifically, a cost-utility analysis includes a measure of morbidity, and cost-effectiveness is expressed as the cost per quality-adjusted life year (QALY) gained (Weinstein & Stason 1977). Many authors do not explicitly distinguish between a cost-effectiveness analysis and a cost-utility analysis. Likewise, in this thesis we will not always make this distinction but instead refer to cost-utility analyses as cost-effectiveness analyses.

Whether or not the investigated intervention or preventive program is cost-effective depends on the value that society places on a gained life year or QALY. In the Netherlands, a commonly applied threshold value for a preventive measure is that a life year (or QALY) is worth €20,000. A cost-effectiveness ratio is estimated for a specific intervention compared to a standard one or no intervention. When that ratio lies below this value, the intervention is considered cost-effective.

Studies of the cost-effectiveness of preventive measures and interventions against infectious diseases have regularly been conducted and published since the beginning of the 1970s. Since the year 2000, the output has risen substantially each year (Willems & Sanders 1981, Kim & Goldie 2008, Miller & Hinman 2009). This kind of studies also plays an important role in allocating society's scarce resources.

Dynamic models, which take herd immunity into account, are increasingly considered warranted to analyze interventions against infectious diseases. Health economists involved in economic evaluations of infectious diseases recognize the importance of dynamic modeling (e.g. Beutels et al. 2002, Brisson & Edmunds 2003). In practice, however, dynamic modeling is not widely used to investigate the cost-effectiveness of interventions and preventive measures (see e.g., Kim & Goldie 2008).

THEME AND OBJECTIVE OF THE THESIS

The objective of this thesis is to explore the cost-effectiveness of controlling epidemics and preventing outbreaks of infectious diseases. Several questions are posed: Which pandemic containment strategies are cost-effective? Would it be cost-effective to screen pregnant women for rubella? Have interventions against pertussis been cost-effective? These questions reflect topics of current interest in the Netherlands and are investigated from a public health perspective.

In the next chapter, we take an international perspective; different vaccination strategies during different pandemic influenza outbreak scenarios are explored for three West-European countries. Then, in Chapter 3, we investigate the cost-effectiveness of stockpiling antiviral drugs. In Chapter 4, we estimate the cost-effectiveness of controlling an influenza pandemic with antiviral drugs, considering the choice of different models. The cost-effectiveness ratios resulting from a dynamic model (which incorporates transmission) are compared to those from a static model (which does not incorporate transmission). Wrapping up the research on cost-effectiveness of interventions against pandemic influenza, the research published so far is reviewed and presented in Chapter 5.

Clusters of unvaccinated individuals form another aspect of public health intervention in the Netherlands. Prevention of congenital rubella syndrome warrants special attention. A cost-utility analysis of a screening and vaccination program for pregnant women in the low vaccination regions is presented in Chapter 6.

Finally, outbreaks of pertussis occur regularly despite high participation in the national immunization program. A booster vaccination was introduced in the Netherlands in 2002 among four-year-olds, with the aim of restoring immunity to protective levels. Chapter 7 presents a cost-utility estimate of the effect of this booster.

In Chapter 8 we discuss our findings and their implications for decision-making. We end by making some general remarks and drawing conclusions.

Chapter 2

Cost-effectiveness of vaccination against pandemic influenza in European countries: The role of immunity in the elderly

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Submitted for publication

INTRODUCTION

Many countries now have preparedness plans to deal with an influenza pandemic. When developing these plans, dynamic epidemiological models have often been used to simulate the effects of intervention (Longini et al. 2004, Longini et al. 2005, Ferguson et al. 2005, Ferguson et al. 2006, Germann et al. 2006, Mylius et al. 2008). Additionally, some cost-effectiveness analyses have been made of attempts to control a pandemic (Sander et al. 2009, Lugnér et al. 2010, Baguelin et al. 2010).

Dynamic models, simulations, and analyses are based on assumptions concerning the transmissibility of the virus, contacts between individuals, length of illness, etc. These assumptions are mainly derived from observations of past influenza pandemics and of seasonal influenza epidemics. One characteristic of a pandemic is that most of the population lacks immunity to the new virus, whereby the virus can infect a substantial proportion of the population. In fact, most dynamic models assume total susceptibility, i.e., the absence of pre-existing immunity. However, soon after the pandemic broke out in the spring of 2009, it was suggested that older people actually did have pre-existing immunity, which had not been taken into account in predictive models so far. This situation could be true and relevant for future pandemics.

The World Health Organization (WHO) and The European Centre of Disease and Prevention Control (ECDC) provide general advice to a wide range of countries on whether or not to vaccinate and how to prioritize pandemic influenza vaccination if the vaccine supply falls short. Yet countries differ in terms of their demographic characteristics, contact patterns, health-care system, and cost structure. This obviously raises the question whether the guidance should be tailored to the national level instead of providing a single recommendation suitable for a range of countries. Also, the situation changes when the main indicators are not only clinical impacts and health risks. When the vaccination policies also take health economics into the picture, what is deemed the best vaccination strategy might differ even more among countries. When economic impacts are included in the decision process, country-specific details are of great significance. With resources being scarce and warranting careful allocation, both for the recent and the next pandemic influenza outbreak, economic aspects are obviously important for decisions of this magnitude. Country-specific details in demography and contact patterns play a role in the transmission of influenza and may cause differences between the cost-effectiveness for countries with slightly different demographic profiles. Specifically, with pre-existing immunity in the older population, the effect on the cost-effectiveness of certain vaccination strategies might be substantial for a country with a high percentage older people. If the influence is large, it might shift the optimal strategy, and a general advice would lose its significance.

This paper investigates which vaccination strategy is the most cost-effective in different pandemic scenarios, including various vaccine-availability options. The question is, which group in the population should be vaccinated to get the highest benefit from the resources spent? Moreover, would a different strategy apply in different countries? The objective of the analysis presented here is to investigate the cost-effectiveness of different vaccination strategies in different pandemic scenarios

for three countries that are geographically and culturally close but differ in regard to population structure.

METHODS

In our general framework, an age-structured transmission model of pandemic influenza that incorporates demographic characteristics, low- and high-risk groups, and social contact patterns was linked to health-care consumption and unit costs for health-care resources that are specific to Germany, the Netherlands, and the United Kingdom (UK).

Model

Transmission model

We used a deterministic age-structured SEIR (Susceptible, Exposed, Infected, Recovered) epidemic model that describes how an influenza A virus will spread in a population (Mylius et al. 2008). Individuals are categorized into six age groups (0-4 years, 5-12 years, 13-19 years, 20-39 years, 40-64 years, 65+ years) and classified as susceptible to infection (S), infected but not yet infectious (E), infected and infectious (I), or as recovered, immune, or dead (R). The infection cycle is modeled by realistic (gamma) distributions for the latent and infectious periods. In particular, by setting the mean latent period to be 1.95 days, the mean infectious period to be 1.6 days, and the variances of the latent and infectious periods at 0.48 and 0.32, respectively, the mean generation interval obtained was 2.8 days. This value corresponds with observed values for seasonal influenza (Wallinga & Lipsitch 2007) and the novel influenza A/H1N1 virus (Hahné et al. 2009). The virus' transmissibility was calibrated to render an overall reproduction ratio of 1.7 in a susceptible population, which is in line with epidemic growth rates observed in past influenza pandemics (Wallinga & Lipsitch 2007).

Social contact patterns

Age-specific contact patterns were calculated from data on self-reported conversational contact rates for Germany, the Netherlands, and the UK in 2006 (Mossong et al. 2008). A summary of the contact rates for the six age categories shows that for all three countries, people primarily tend to mix within their own age group (Appendix Chapter 2 Table A2.1).

Demographic data

The population size by age group was set at that for 2006, as obtained from official sources: Federal Statistical Office for Germany; Statistics Netherlands; and UK National Statistics. No official projections of remaining life years for 2009 were available for Germany. The remaining life years for Germany were projected from

2007 to 2009 on the basis of the percentage increase between 2005 and 2007 per age group.

Low- and high-risk groups

Each age group was divided into two subgroups, one with average-risk individuals and one with individuals at a high risk of developing serious complications upon infection. High-risk groups include immunocompromised individuals, people with chronic respiratory diseases, and all people over 65 in nursing homes. The share of the population in each age and risk group is based on detailed data available for the Netherlands (van Genugten et al. 2003). Since we could not find any information at this level of detail for the other two countries, we used the Dutch data for the other two countries (Table 2.1).

Table 2.1 Demographic data for the Netherlands, Germany, and the United Kingdom

		Age group					
	Total population	0-4	5-12	13-19	20-39	40-64	65+
Germany	82314906						
Percentage in age group		4%	9%	7%	25%	35%	20%
Share of population in high-risk group		0.033	0.027	0.029	0.064	0.061	0.256
Remaining life years[a] [1] (average in age group)		78.41	72.03	64.58	51.36	30.18	8.37
Netherlands	16357992						
Percentage in age group		6%	11%	7%	26%	35%	14%
Share of population in high-risk group		0.024	0.021	0.027	0.061	0.062	0.349
Remaining life years [2] (average in age group)		78.73	71.94	64.50	51.24	29.91	8.47
United Kingdom	60587800						
Percentage in age group		6%	11%	8%	27%	32%	16%
Share of population in high-risk group		0.024	0.022	0.025	0.059	0.066	0.316
Remaining life years [3] (average in age group)		78.55	72.21	64.76	51.60	30.47	9.59

Sources: [1] https://www-genesis.destatis.de; [2] http://statline.cbs.nl/statweb/; [3] http://www.gad.gov.uk

Note: Age-group-specific share of the population in the high-risk group is based on van Genugten et al. (2003);
a. No official projections for 2009 were available. The remaining life years for Germany are inflated from 2007 to 2009 by the percentage increase between 2005 and 2007 per age group. Remaining life years in Table 2.1 are not discounted.

Pandemic scenarios

We evaluated a number of plausible scenarios for an influenza pandemic. In an optimistic scenario it is possible that a vaccine can be produced against the new virus and that a large number of vaccine doses would be available before the pandemic takes off. We will refer to scenarios where individuals can be vaccinated prior to the peak of the pandemic (thus, at the start) as "early" vaccination. In a more pessimistic scenario the same number of doses would become available during the pandemic and vaccination takes place at its peak. We will refer to scenarios where individuals are vaccinated at the peak of the pandemic as "late" vaccination. Because an influenza pandemic is caused by a novel virus, it is very well possible that all individuals in the population are susceptible to infection with the virus. We will refer to scenarios where all individuals are completely susceptible at the start of the pandemic and before vaccination starts as "no immunity". As observations during the Asian influenza pandemic (Mulder & Masurel 1958) and the recent pandemic in 2009 (Miller et al. 2009) have shown, it is also possible for older individuals in the population to have partial cross-immunity to the novel virus. We will refer to scenarios where some older individuals are protected from infection at the start of the pandemic and before vaccination starts as "pre-existing immunity". The precise values of variables and parameters in each of these scenarios are given in Table 2.2.

Vaccination strategies

For each of the scenarios we investigated four alternative strategies to allocate the available vaccines over the various age groups. The first one is to not vaccinate at all; we will refer to this strategy as "no vaccination". The second is to vaccinate everyone who is eligible for vaccination; we will refer to this strategy as vaccinating "the whole population". The third is to vaccinate almost all of the elderly; we will refer to this one as vaccinating the "elderly". The fourth strategy is to vaccinate primary and secondary school children in the age groups 5 - 19; we will refer to this one as vaccinating "high transmitters". These young groups are responsible for a substantial part of the transmission, as they have relatively more contacts (Appendix Chapter 2 Table A2.1). The precise percentages of vaccine uptake in these strategies are provided in Table

Table 2.2 Description of four scenarios for an influenza pandemic

Availability vaccine	Immunity scenario	Proportion immune at start of pandemic					
		0-4	5-12	13-19	20-39	40-64	65+
Early (Prior to peak)	No immunity	0	0	0	0	0	0
	Pre-existing immunity	0	0	0	0	0.3	0.5
Late (Peak of pandemic)	No immunity	0	0	0	0	0	0
	Pre-existing immunity	0	0	0	0	0.3	0.5

2.3. Because not all of the people who are eligible for vaccination will be vaccinated, we assume that vaccination coverage is at most 90%. The lower vaccination percentage in the youngest age group of 0 - 4 takes into account the fact that pandemic influenza vaccine is not registered for infants under 6 months of age (Table 2.3).

Vaccination efficacy

We focused on an imperfect all-or-nothing vaccine. This means that, with a certain probability, it provided either perfect protection from infection or none at all (primary vaccine failure). The efficacy of the vaccine (i.e., the probability that the vaccine provided protection from infection) is set at 80% for the ages 0-64 years. For persons 65 years or older, the vaccine efficacy is assumed to be 56% (Gross et al. 1995). We made no distinction between high- and low-risk individuals regarding the efficacy.

Cost-effectiveness

We calculated the cost per quality-adjusted life year (QALY) gained as the incremental cost-effectiveness ratio (ICER) between the specific intervention strategy and the non-intervention option. This means that the cost that the intervention (the vaccination) entails minus the saved health-care costs due to the intervention is divided by the gain in QALYs between the non-intervention and the intervention options. The resulting ratio is more cost-effective the lower it is. Beneath a (country-) specific threshold value, it is deemed cost-effective and as potentially justifying the intervention (€30,000 for Germany; €20,000 for the Netherlands; £30,000 (€37,800) for the UK).

Health-care use

It was assumed that 60% of the infected persons developed influenza-like illness (ILI) and that the rest were asymptomatic (Jordan Jr. et al. 1958, Fukuda et al. 2004). A proportion of the symptomatic individuals seek medical help. The following types of health-care consumption are included in the calculations: over-the-counter (OTC)

Table 2.3 Proportion vaccinated for each vaccination strategy scenario in each age group

Vaccination strategy	Vaccination coverage, %					
	0-4	5-12	13-19	20-39	40-64	65+
No vaccination	0	0	0	0	0	0
Whole population	54	90	90	90	90	90
Elderly	0	0	0	0	0	90
High transmitters	0	90	90	0	0	0

drug use; general practitioner (GP) visits; prescription medication (in particular, antibiotics to prevent or treat secondary infections); and hospitalizations (in normal (85%) and intensive-care (15%) units). Persons with ILI were assumed to receive antiviral drugs if in contact with a GP, but we did not assume any influence on transmission or complication rates. Hospitalization rates were based on Dutch data but were applied to all three countries (Appendix Chapter 2 Table A2.2) (Baltussen et al. 1998).

Costs

Country-specific cost data for resource use and percentages of ILI cases using the specific health-care resources were gathered from the published literature. Where no specific data for Germany or the UK were found, data available for the Netherlands were taken as a proxy. Vaccine costs are mainly unknown and were based on unofficial sources. A two-dose schedule was assumed, and it was the same for all three countries. All costs were recalculated to reflect 2008 price levels. These were expressed in euros (€) using the average exchange rate between the euro and the pound sterling over the year 2008 (Table 2.4). Costs were not discounted due to the relatively short time perspective of the analysis regarding resource and financial impacts.

Indirect costs for production losses should be included in cost-effectiveness analysis, according to the Dutch guidelines, and estimated using the friction costing approach (Oostenbrink et al. 2003). In the German guidelines, the analyst's perspective determines whether or not to include indirect costs. According to the UK guidelines, in contrast, the perspective of the payer is required; i.e., production losses should not be included (ISPOR website). We thus calculated production losses for ILI cases using the friction cost method for the Netherlands and the human capital approach for the other two countries. The main differences between the two methods are as follows: the human capital method estimates a potential value of lost production due to absenteeism or death, while the friction cost method suggests that the production losses might be smaller. Due to replacement of long-term absent (or deceased) employees, and the assumption that short-term absenteeism will be partly caught up with when the sick employee returns to work, absent employees only contribute to the production losses during the "friction period" until he or she is replaced (Koopmanschap et al. 1995). Taking a conservative approach, we estimated production losses for deaths using the friction cost method for all countries. Furthermore, we present the cost-effectiveness ratio both with and without indirect costs.

Quality of life and life years lost

Our estimates of losses in quality of life due to an influenza episode were based on burden-of-disease estimates for the Netherlands (Melse et al. 2000) for the scenario "no immunity". During the 2009 pandemic, estimates of quality of life were gathered in the UK (Baguelin et al. 2010). These weights were used for the scenario "pre-existing immunity", reflecting the burden of illness due to the 2009 pandemic

Table 2.4 Health-care consumption, unit costs, probability of use, production loss per day, and length of absence due to illness, € 2008 prices

	Netherlands		Germany		United Kingdom	
	Unit cost	Consumption units or probability of use (%)	Unit cost	Consumption units or probability of use (%)	Unit cost	Consumption units or probability of use (%)
Direct costs						
Vaccine and administration costs	16[a,b]	2 doses	16[a,b]	2 doses	16[a,b]	2 doses
GP visits if ILI	21.80 [1]	24% [2]	9.70[5]	24% [2]	44.40 [4]	24% [2]
Antibiotics if GP	6.90[a] [3]	20% [3]	20.50[5]	17.5% [5]	9.60 [6]	20% [3]
Oseltamivir if GP[b]	21 [7]	Treatment course	21[7]	Treatment course	21 [7]	Treatment course
OTC drugs if ILI	6.30 [3]	80% [3]	6 [3]	80% [3]	7.30 [6]	80% [3]
Hospitalization episode	3398 [1]		4075 [5]		2892 [3]	
Production losses						
Ages 20-40 (per day)	213 [3]	-	233 [5]	-	118 [4]	-
Ages 40-65 (per day)	255 [3]	-	233 [5]	-	132 [4]	-
Days of absence (all ages)	-	3.25 [3]	-	2.16 [5]	-	2.9 [4]

Note: When country-specific data are missing, Dutch data are used for the other countries; ILI=influenza-like illness; GP=general practitioner;
a. per dose including administration costs (Postma et al. 2005); b. assumed the same for all three countries; prices updated to 2008 using country-specific CPI-index.

Sources: [1] Oostenbrink et al. 2004; [2] van Genugten et al. 2003; [3] Postma et al. 2005; [4] Personal communication: K. Tolley; [5] Aballéa et al. 2007; [6] Sander et al. 2006; [7] www.medicijnkosten.nl.

virus. For hospitalized cases we used quality-of-life estimates that were 2.17 times higher than for ILI, again following the example of Baguelin et al. (2010) (Table 2.5).

The remaining life years that we used in the economic calculations to estimate QALYs gained were based on predictions made for 2009. The number of remaining life years at a specific age was based on national predictions for 2009 (Table 2.1). These were calculated with a weighting factor for the high- and low-risk group. The low-risk group was weighted with a factor of 1.15 and the high-risk group with 0.75, reflecting a longer expected remaining lifetime for a healthy individual compared to someone with chronic conditions (Postma et al. 1999). We used the same case fatality rate for all three countries, estimated as three age-group-specific excess death rates due to influenza (Appendix Chapter 2 Table A2.2) (Sprenger et al. 1993). For the economic evaluation, life years were discounted at country-specific rates, according to the respective guidelines: Germany at 5%; the Netherlands at 1.5%; and the UK at 3.5%.

RESULTS

The clinical attack rate (CAR) for an uncontrolled influenza pandemic is very similar in the three countries included here. The scenario where the total population is assumed to be equally susceptible results in an overall CAR of about 36%. When adjusting for pre-existing immunity, the overall CAR is about 27%.

The ICERs comparing each strategy for each scenario, where vaccination is compared to no vaccination, are presented in Figure 2.1. As can be seen there, all these ICERs are below country-specific thresholds. Furthermore, the ICERs are shown with and without production losses. If indirect costs are included in the calculations, most scenarios are cost-saving (in which case there is no visible bar in Figure 2.1 at the specific strategy). There are however a few exceptions where vaccination is not cost-saving when including indirect costs. If there is "pre-existing immunity" among the older population, vaccinating only the "elderly" is not cost-saving, neither at an "early" nor at a "late" stage in the pandemic. Furthermore, when the vaccine becomes available "late" in the pandemic, vaccinating only the "elderly" is not cost-saving if there is "no immunity". In the UK, vaccinating the "whole

Table 2.5 One-year losses in quality of life due to influenza infection

Loss in quality of life for one year	Seasonal Influenza	2009 A/H1N1 pandemic influenza	
		Adults	Children (<18 years)
Influenza infection	0.01 [1]	0.0074 [2]	0.0082 [2]
Influenza infection with hospitalization	0.0217 [2]	0.016 [2]	0.018 [2]

Sources: [1] Melse et al. (2000), [2] Baguelin et al. (2010)

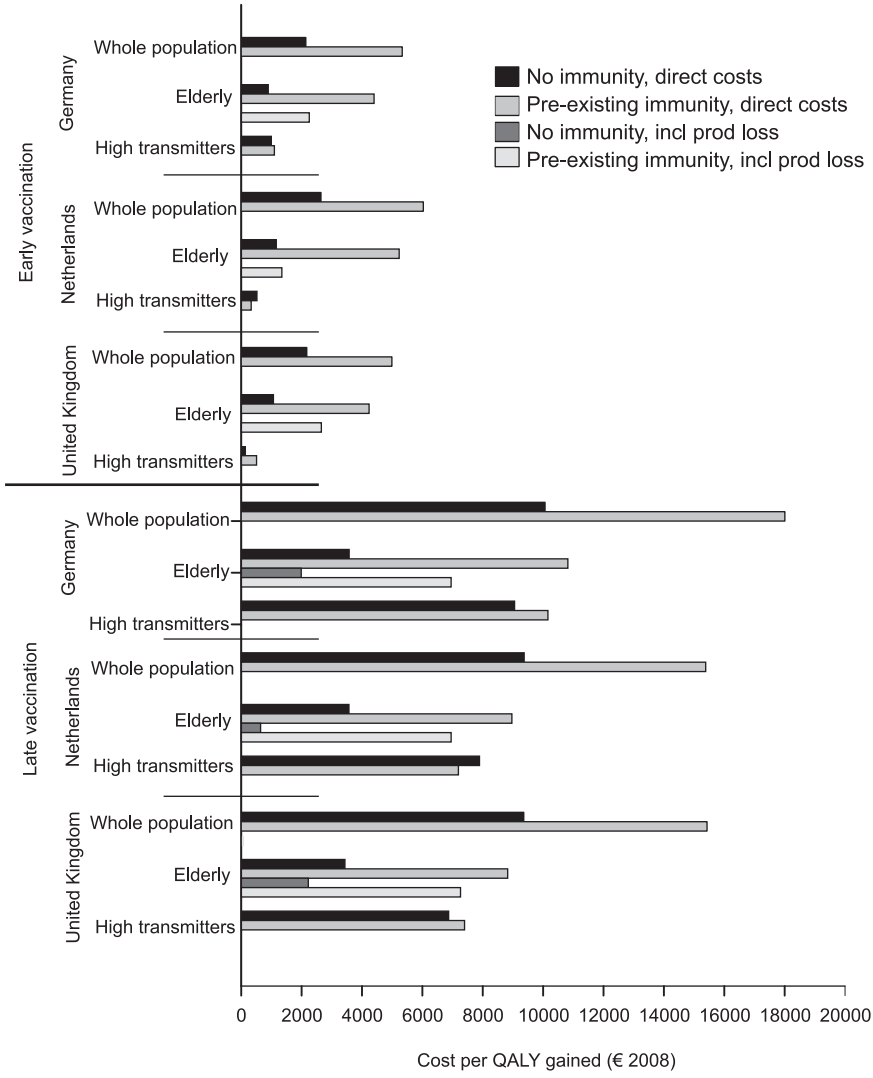

Figure 2.1 Incremental cost-effectiveness ratios of vaccination strategies and scenarios ("early" or "late" availability of vaccine; "no immunity" or "pre-existing immunity" in the elderly) in three countries (Germany, the Netherlands, the United Kingdom)

population" "late" in the epidemic would not be cost-saving, unlike the other two countries.

All vaccination strategies are less cost-effective when there is pre-existing immunity in the elderly population than is the case when the whole population is

susceptible. That is, the cost-effectiveness ratio is higher. This pattern is similar for all three countries.

Depending on which pandemic scenario we are looking at, the most cost-effective vaccination strategy would be different (Table 2.6). For instance, vaccinating "high transmitters" is the most cost-effective strategy in the scenario "pre-existing immunity" for all countries, and it does not matter if the vaccine is available "early" or "late" in the pandemic.

Vaccinating the "elderly" is the most cost-effective strategy for the scenario "no immunity" when the vaccine becomes available "late" in the pandemic. In the scenario "no immunity" and if vaccine is available "early" in the pandemic, vaccinating the "elderly" is the most cost-effective strategy in Germany, whereas vaccinating "high-transmitters" is the optimal strategy for the other two countries.

Table 2.7 presents a detailed composite picture of ICERs split into age groups. It is intended to illustrate that the vaccinated age group is not necessarily the one in which costs are saved or QALYs gained. In Table 2.7 the vaccination costs and cost savings due to vaccination (net costs) attributed to each age group are divided by the QALY gained in that age group. It shows the results for the two vaccination strategies, i.e., vaccinating the "elderly" and "high-transmitters". The ICERs for "all ages" in Table 2.7 are the cost per QALY gained at the population level.

Clearly, the ICER within a vaccinated age group is higher than the "all ages" ICER. This is seen, for instance, in the scenario where the vaccine is available "late" in the pandemic and "high transmitters" are vaccinated (similar for all countries). Vaccinating high-transmitters entails costs for the vaccination program itself, and the costs saved in these age groups (5-12 and 13-19) do not exceed the costs of vaccinating them. However, transmission is reduced, leading to cost savings in other age groups.

DISCUSSION

We wanted to know which vaccination strategy would be the most cost-effective for different influenza pandemic scenarios and if that strategy differed among countries.

Table 2.6 Most cost-effective vaccination strategy, per country

Availability vaccine	Immunity scenario	Germany	Netherlands	United Kingdom
Early	No immunity	Elderly	High transmitters	High transmitters
	Pre-existing immunity	High transmitters	High transmitters	High transmitters
Late	No immunity	Elderly	Elderly	Elderly
	Pre-existing immunity	High transmitters	High transmitters	High transmitters

Table 2.7 Cost per QALY (incremental cost-effectiveness ratio between the vaccination strategy and non-intervention) for two scenarios and two vaccination strategies. (Direct health-care costs, € 2008)

		All ages		0 – 4		5 – 12		13 – 19		20 – 39		40 – 64		65+	
		Elderly	High trans-mitters	Elderly	High trans-mitters	Elderly	High trans-mitters	Elderly	High trans-mitters	Elderly	High trans-mitters	Elderly	High trans-mitters	Elderly	High trans-mitters
Germany															
Early	No immunity	900	1000	cs	cs	cs	6760	cs	5540	cs	cs	cs	cs	1010	cs
	Pre-existing immunity	4400	1100	cs	cs	cs	10130	cs	7920	cs	cs	cs	cs	5048	900
Late	No immunity	3570	7900	cs	cs	cs	23120	cs	26080	cs	cs	cs	cs	3800	cs
	Pre-existing immunity	8970	7200	cs	cs	cs	28160	cs	29530	cs	cs	cs	cs	10670	cs
Netherlands															
Early	No immunity	1160	520	cs	cs	cs	4540	cs	4340	cs	cs	cs	cs	1330	cs
	Pre-existing immunity	5230	330	cs	cs	cs	5700	cs	5440	cs	cs	cs	cs	5720	cs
Late	No immunity	3580	9060	cs	cs	cs	23560	cs	27020	cs	cs	cs	cs	3870	cs
	Pre-existing immunity	10820	10160	cs	cs	cs	28730	cs	33180	cs	cs	cs	cs	11670	cs
United Kingdom															
Early	No immunity	1070	170	cs	cs	cs	13340	cs	9660	cs	1670	cs	1700	1230	cs
	Pre-existing immunity	4240	510	cs	cs	cs	cs	cs	9620	cs	2350	cs	cs	4610	cs
Late	No immunity	3440	6880	cs	cs	cs	23420	cs	23500	cs	cs	cs	cs	3720	cs
	Pre-existing immunity	8830	7400	cs	cs	cs	26960	cs	26760	cs	cs	cs	cs	9450	cs

cs=cost saving

To find out, we evaluated the cost-effectiveness of four intervention strategies (including no vaccination) for four pandemic influenza scenarios ("early" or "late" availability of vaccine; "no immunity" or "pre-existing immunity" in the elderly) in three countries (Germany, the Netherlands, the UK). We found that the most cost-effective strategy does differ across pandemic scenarios and to some extent among countries. At the population level, all vaccination strategies are cost-effective (incremental cost per QALY gained, comparing intervention to non-intervention).

For one scenario – when there is "no immunity" and when the vaccine is available "late" in the pandemic – the optimal strategy is to vaccinate the elderly. For the other three scenarios, we found that it is the most cost-effective to vaccinate young people aged 5-19 years, the high transmitters. However, there is one exception to this pattern: in Germany, vaccinating the elderly would still be more cost-effective than vaccinating the high transmitters in the scenario "no immunity" and "early" vaccination. Part of the explanation lies in the population profile. In Germany about 20% of the population is 65 years or older, compared to about 15% in the Netherlands and the UK. In this age group there is a higher proportion with a high risk of complications. Preventing complications means that costs can be saved, thereby improving the cost-effectiveness of the intervention.

So far, no pandemic preparedness models of the cost-effectiveness of different vaccination strategies have incorporated a possible pre-existing immunity in the elderly or other age groups. Since pre-existing immunity seemed to have played a part in the recent 2009 pandemic, we incorporated it in one scenario. If a future pandemic virus is related to the A/H1N1 virus, there could be a possible pre-existing immunity then too. We expected the role of pre-existing immunity to decrease the cost-effectiveness of all vaccination strategies. We also expected that this decrease would be more pronounced in a country where the proportion of people in the older age groups was higher, in this case Germany. The fact that we have demonstrated these tendencies enhances the face validity of our model and its results. Thus, our complex model helps us understand that country-specific differences in variables such as the demographic profile will lead to differences in ranking vaccination strategies based on cost-effectiveness.

In the countries included in this analysis, the annual vaccination of healthy people above 65 (or 60) years of age and groups at high risk of complications from influenza is common practice. These two groups were generally the first to be vaccinated during the recent pandemic. We did not specifically address the cost-effectiveness of vaccinating only high-risk groups. The main reason is the minor influence it would have on transmission in those groups. We were more interested in the influence of transmission on cost-effectiveness. Moreover, in the strategies involving the oldest age group, where the largest proportion of people with other health conditions and chronic diseases are seen, the vaccine uptake was set to 90%. The influence on the cost-effectiveness ratios of including the vaccination of high-risk groups among the younger age groups was presumed to be minor. Furthermore, we did not have any detailed data on the share of the population in a high-risk group for each country. We were thus forced to apply the share known for the Netherlands to the other two

countries. How such country-specific data would have influenced the results is difficult to say.

Our analysis shows that the use of dynamic modeling is crucial when studying a transmittable disease such as influenza since it captures the herd immunity effect. The latter means that when a large proportion of the population is immune – through vaccination, for instance – the likelihood that a susceptible person will come into contact with an infected individual is lowered. As a consequence, the susceptible person is indirectly protected against disease. An earlier study to determine the optimal strategy for distributing a vaccine against a pandemic influenza virus used a static model that did not take transmission into account (Meltzer et al. 1999). The option of vaccinating children and young adults was not even considered. When vaccinating only young people, the intervention may not be cost-effective if we only look at the costs and effects in that group, as we have shown. Including effects and cost-savings at the population level changes the cost-effectiveness of the intervention, since other age groups benefit from reduced transmission. We have added to the understanding of this indirect benefit and shown that it influences cost-effectiveness. From a policy perspective, this is vital information.

We did not attempt to calibrate this model to the recent 2009 influenza pandemic, as we did not seek to generate the exact outcomes registered for this pandemic. Some economic evaluations of vaccination strategies have been made during the recent pandemic using dynamic models. In Ontario (Canada) it was assumed that the vaccination coverage was 30% within the population. It was shown that the vaccination strategy was cost-effective (less than CAN $5,000 per QALY gained) (Sanders et al. 2009). In the UK, a transmission model was fitted to the data from the recent pandemic. There, a probabilistic economic model revealed a high probability that vaccinating high-risk groups was cost-effective; 98% of the simulations resulted in an ICER that was less than GB £30,000 per QALY gained (Baguelin et al. 2010). Notably, in these simulations the cost of the vaccine was not included but instead seen as a sunk cost. If vaccine costs had been included, the probability that vaccinating high-risk groups was cost-effective would have been less than 50%.

Our primary intention with this research was to investigate the extent to which cost-effectiveness estimates of certain vaccination strategies are affected by assumptions about the pre-existing immunity that was seen during the recent influenza pandemic and to study the impact of the availability of an effective vaccine. Secondly, we wanted to compare the strategies of countries with a similar cultural background to examine the usefulness of a general advice on vaccination strategy. The implications for ascertaining which strategy would be optimal are of great importance in policy-making. We conclude that the particular pandemic scenario seems to be of more importance than the demographic and country-specific health-care and health-economic data for these countries. A general recommendation from an international organization, such as the WHO or the ECDC, may be useful when comparing cost-effectiveness for culturally similar countries but should be considered with due caution. Under some circumstances – for instance, when the demographics are different in the countries compared – pre-existing immunity can change the

cost-effectiveness of intervention. With an aging population, this could be of crucial importance for the mitigation of a future pandemic caused by an influenza A/H1N1 virus.

Acknowledgement

This research was partly funded by a Quantitative Immunization and Vaccine Related Research (QUIVER) grant from the World Health Organization.
We thank Dr. Jan van de Kassteele for calculating the contact matrices.

APPENDIX CHAPTER 2

Table A2.1 Age-specific mixing matrices

	Germany					
	0–4	5–12	13–19	20–39	40–64	65+
0–4	0.66	0.13	0.06	0.17	0.07	0.04
5–12	0.13	0.53	0.15	0.10	0.08	0.03
13–19	0.06	0.15	1.00	0.13	0.10	0.02
20–39	0.17	0.10	0.13	0.24	0.11	0.04
40–64	0.07	0.08	0.10	0.11	0.15	0.06
65+	0.04	0.03	0.02	0.04	0.06	0.13
	Netherlands					
	0–4	5–12	13–19	20–39	40–64	65+
0–4	0.43	0.13	0.01	0.09	0.04	0.01
5–12	0.13	0.79	0.13	0.06	0.06	0.02
13–19	0.01	0.13	1.00	0.06	0.07	0.03
20–39	0.09	0.06	0.06	0.18	0.10	0.04
40–64	0.04	0.06	0.07	0.10	0.13	0.05
65+	0.01	0.02	0.03	0.04	0.05	0.13
	United Kingdom					
	0–4	5–12	13–19	20–39	40–64	65+
0–4	0.37	0.12	0.06	0.13	0.06	0.02
5–12	0.12	0.80	0.15	0.12	0.08	0.03
13–19	0.06	0.15	1.00	0.13	0.10	0.06
20–39	0.13	0.12	0.13	0.20	0.12	0.05
40–64	0.06	0.08	0.10	0.12	0.14	0.08
65+	0.02	0.03	0.06	0.05	0.08	0.12

Note: The matrices are used to determine the rates of transmission between different age groups and are estimated with data on human social contact patterns (Mossong et al. 2008). To emphasize the relative differences among the countries, the matrices shown here have been normalized so that the largest element of each matrix equals 1. In the model the overall transmission rates were calibrated so that the basic reproduction ratio has a specific predefined value (see Wallinga et al. 2006 for details).

Table A2.2 Proportion of infection in risk groups and probability of complications (hospitalizations and deaths) given infection

		Age groups					
		0-4	5-12	13-19	20-39	40-64	65+
Proportion of total population	high risk	0.0014	0.0023	0.0020	0.0162	0.0215	0.0506
	low risk	0.0577	0.0951	0.0835	0.2478	0.3278	0.0942
Probability of hospitalization	high risk	$8.70*10^{-3}$	$8.70*10^{-3}$	$8.70*10^{-3}$	$1.29*10^{-2}$	$1.29*10^{-2}$	$3.36*10^{-2}$
	low risk	$3.45*10^{-5}$	$3.45*10^{-5}$	$3.45*10^{-5}$	$4.31*10^{-5}$	$4.31*10^{-5}$	$5.85*10^{-3}$
Probability of death	high risk	$3.44*10^{-4}$	$3.44*10^{-4}$	$3.44*10^{-4}$	$5.11*10^{-4}$	$5.11*10^{-4}$	$1.69*10^{-2}$
	low risk	$1.47*10^{-5}$	$1.47*10^{-5}$	$1.47*10^{-5}$	$1.83*10^{-5}$	$1.83*10^{-5}$	$3.21*10^{-3}$

Source: Genugten et al. (2003)

Chapter 3

Investment decisions in influenza pandemic contingency planning: Cost-effectiveness of stockpiling antiviral drugs

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European Journal of Public Health 2009; 19: 516-520

INTRODUCTION

In 1918–19 an influenza pandemic hit the world in three waves. Mainly the second wave led to exceptionally elevated loss of lives, with the unique pattern involving the highest case fatality among the otherwise healthy young population (20-40 years of age) (Taubenberger & Morens 2006, Potter 2001). Without all details about the origin of the virus yet (or ever) being known, the A/H1N1 virus from the 1918 pandemic has been shown to be a distantly related avian virus. The viruses causing two later pandemics (the Asian flu in 1957-58 and the Hong-Kong flu in 1968-69) were both related to the 1918-pandemic virus but with substantially lower case fatality rates (Taubenberger & Morens 2006).

The cross-species transmission to humans of the avian influenza A/H5N1, circulating among wild and domesticated birds for a few years now, already raised concern about the possible occurrence of another influenza pandemic, should this virus acquire human-to-human transmission abilities. Another virus has recently raised additional concern about such a pandemic. In particular, by the end of April 2009 the World Health Organization (WHO) raised the level of influenza pandemic alert to phase five (out of six) due to the recent spread of the new influenza virus A/H1N1. Daily details of the outbreak can be found on the WHO website (May 2009).

One strategy to minimize the consequences of a pandemic for public health and the economy is to mitigate the spread and the health consequences by therapeutic treatment with anti-viral (AV) drugs, advocated amongst others by the Dutch authorities (Health Council of the Netherlands 2005). To be able to provide the population with these drugs in sufficient quantities and timely, stockpiling is necessary (Radonovich et al. 2009). Yet, such an investment raises the question whether such large scale stockpiling is cost-effective, i.e., whether society's scarce resources are efficiently spent. There are only a few studies yet published, investigating the cost-effectiveness of stockpiling AV-drugs (Balicer et al. 2005, Lee et al. 2006, Siddiqui et al. 2008). All these calculations assume a clinical attack rate (CAR) of about 25-30% and that there would be a pandemic within 30 years. These assumptions may be conceived as realistic, as indeed three pandemics were seen during the last 100 years, all with CARs in that order of magnitude (Nguyen-Van-Tam & Hampson 2003). Yet, of course exact occurrences in the future remain inherently uncertain.

One aspect of AV-therapy is the impact on the transmission of influenza. This can only be adequately modelled with a dynamic model, taking the force of infection explicitly into account. With such a model the effect of AV-therapy and other containment methods on the CAR can be estimated in detail and changing over time (Ferguson et al. 2005, Longini et al. 2005, Mylius et al. 2008, Ferguson et al. 2006, Germann et al. 2006, Epstein et al. 2007, Sander et al. 2008). One of these included costs for stockpiling, showing that this strategy would be cost-effective for the USA at a – relatively high - predicted CAR of 50% (Sander et al. 2008).

Influenza pandemics are a continuous threat to public health. As long as there is no strain-specific, or universal, vaccine against pandemic influenza, the question

whether to stockpile AV-drugs remains relevant. This certainly includes the cost-effectiveness aspects which requires regular updating, especially when new information about the seriousness of an infection becomes available.

The aim of this study is to estimate whether stockpiling of AV-drugs is cost-effective for therapeutic use in the Netherlands, explicitly taking both a perceived risk of an influenza pandemic and multiple stock turnovers into account. The calculations of the effect of the therapy are based on a dynamic transmission model enabling sensitivity analyses on the effects of alternative CARs and percentages of the population receiving AV-therapy on transmission and cost-effectiveness.

METHODS

Time perspective of the analysis and risk of pandemic

We choose a time horizon of 30 years for our model design. A 30-year horizon reflects an inter-pandemic period based on the three influenza pandemics during the 20th century. This implies that on average a stock would have to be kept during 30 years. Also, the earlier analyses of stockpiling are mostly based on the assumption of an average yearly risk of a pandemic of 3% (3 pandemics in 100 years). Assuming that the risk of a pandemic is independent of the year before, the probability of it occurring during a specified time interval can be approximated by a Poisson distribution; we refer to this as the observed risk. According to the assumption of an annual risk at 3% the estimated risk that there would be at least one pandemic during the 30-year period that was modelled would be 59%, with a predicted risk of one, two and three outbreaks at 37, 16 and 5%, respectively.

The stock turnover depends on stock composition, the shelf-life of the drugs stored and on the time horizon of the analysis. The exact shelf-life of the stock-piled AV-drugs depends on how they are stored. One option is to use bulk powder oseltamivir, a neuraminidase inhibitor with an expected shelf-life of ten years. Another option is to stockpile ready-to-use oseltamivir (Tamiflu®) tablets, with a more limited shelf life of five years. In particular, two stockpiling options are investigated in this analysis: (i) as bulk powder (oseltamivir alone) and (ii) as a combination of 2/3 of bulk-powder and 1/3 of Tamiflu® (combination oseltamivir and Tamiflu®). The combination option is the one previously chosen in the Netherlands, and has already been stockpiled. Currently, the stock consists of five million doses. Over a 30-year horizon, the stock of Tamiflu® would have to be renewed four times, whereas the oseltamivir has to be renewed two times after the first investment.

Costs of treatment and stockpiling

Health-care utilization, sick-leave and deaths were estimated for both the non-intervention and the intervention scenario and subsequently compared in an

incremental cost-effectiveness analysis, based on a dynamic transmission model (Lugnér et al. 2010). In the intervention scenario individuals with influenza symptoms were therapeutically treated with AV-drugs. Treatment was assumed to start within 48 hours of the onset of symptoms, leading to a 50% reduction of health-care resource use due to complications, and a 50% reduction in deaths (Stiver 2003, Kaiser et al. 2003). Outpatient health-care utilization was based on opinions from an expert panel (Genugten et al. 2003).

Table 3.1 Data for use in cost-effectiveness analysis of stockpiling of antiviral drugs, base case analysis (30 year perspective), 80% of population receive AV therapy

	Non-intervention	Intervention	Incremental costs or LYG
Infected individuals	10369872	8594056	
Symptomatic individuals	6221923	5156433	
Hospitalizations	22941	13851	
Deaths	9012	5362	
Life-years lost (discounted)	96795	57912	38883
Costs health care			
Outpatient GP-visits	€33240996	€16529133	€16711863
OTC-drugs and antibiotics due to complications	€37730543	€29235472	€8495071
Hospitalizations	€108334422	€65406635	€42927786
Production losses	€2521537242	€636309973	€1885227269
Costs during pandemic			
Telephone calls to general practitioner		€44077556	- €44077556
Pharmacy fee for AV-prescriptions		€25867972	- €25867972
Stockpiling costs[a] (5 million doses)			
One time purchase, oseltamivir		€45736179	
One time purchase, combination Tamiflu® and oseltamivir		€56185269	
Yearly storing costs		€51389	
30 years stockpiling, PV			
Purchase and storing, oseltamivir		€143658011	
Purchase and storing, combination		€176881136	
Average PV: costs during pandemic			- €1085347
Average PV: savings including productivity losses during pandemic			€1130112974
Average life-years gained			31594
Average quality adjusted life-years gained			48540

a. Assumptions based on estimates from national experts in pandemic preparedness.
LYG = life years gained, PV= present value

Direct health-care costs that occur during a pandemic included telephone contact with an out-patient health-care centre or general practitioner (GP) for a prescription of the AV-drug. Cost savings were expected when treated with AV-drugs, concerning less GP-visits, antibiotics treatments of complications, costs for over-the-counter medications and costs for hospitalizations due to severe complications of influenza. To reflect a societal perspective, productivity losses were included. These were estimated according to the Dutch guidelines using the friction-costing method, an alternative to the human capital method (CVZ 2006, Koopmanschap et al. 1995) (Table 3.1).

Next to the costs for purchase, the costs of stockpiling and opportunity costs were included. Costs for storing reflected heating/cooling of the storage room, electricity, regular inspection and control of the active substance and security arrangements. These storing costs were modelled as equally large annual payments. The stockpiling costs were calculated over the full time horizon of 30 years. By investing in a stock, resources that could have been used for other purposes are tied up. To reflect this opportunity cost, 4% of the investment cost was added (purchase and storing costs). Unused, out-of-date stock is wasted at no cost assumed.

Due to lack of information, some costs had to be neglected (for example, costs for distribution of drugs to pharmacies from the central storing location and costs of dispensing the bulk powder into consumption doses). As a consequence, the costs for the AV-drugs may be slightly underestimated. These costs were investigated in a targeted sensitivity analysis. All costs were expressed in € 2007, costs were discounted with 4% and life-years gained with 1.5% (CVZ 2006). Ergo, the analysis was made from a societal perspective including all relevant costs when available.

Transmission model

The virus transmission during an influenza pandemic was estimated with a dynamic model. A detailed description of the model and its parameters can be found in Lugnér et al. (2010). In the model (Figure 3.1), individuals start as being susceptible and upon infection they progress through a succession of stages, including being infected but not infectious (latent), being infected and infectious, recovered and immune

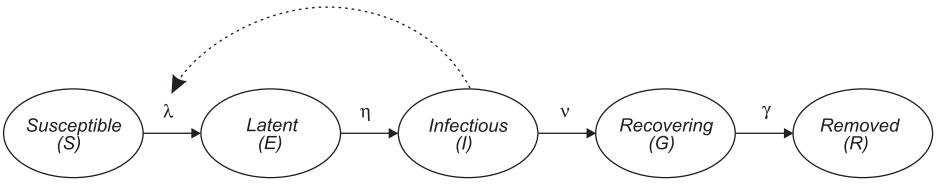

Figure 3.1 Schematic illustration of the dynamic model

Note: λ = rate of becoming infected (force of infection), η = rate of becoming infectious, ν = the rate of losing infectiousness, γ = rate of recovery or death (See Appendix Chapter 4 for further details).
Source: Lugnér et al. 2010

(removed). The model includes key epidemiological parameters, such as contact rates among and within age groups, the length of the infectious period and the probability of transmission of the virus during a contact. The use of AV-drugs affected the recovery rate of patients and the mean infectious time was assumed to be halved. At the start of the first pandemic wave, the whole population was assumed to be susceptible to infection with the virus. In the calculations it was assumed that the pandemic virus behaves as a seasonal influenza virus in the sense that risk of symptoms, risk of illness and risk of death upon infection are similar to those risks observed for seasonal influenza.

The basic reproduction number, or reproductive ratio R_0, reflects a key epidemiological variable which describes how many secondary cases of infections are caused by one primary case in a fully susceptible population (see e.g. Keeling & Rohani 2008). The estimate of R_0 used in the model at 1.73, was based on data from the Asian Flu in 1957 (Wallinga et al. 2006). Of all infected individuals, 60% were assumed to develop clinical symptoms (Jordan Jr. et al. 1958, Fukuda et al. 2004). In the base-case non-intervention scenario the CAR predicted by the dynamic model equals 38%.

Cost-effectiveness ratio

Costs for renewal of the stock were included for the total period, regardless of the occurrence of an outbreak. The costs for the AV-drugs and the savings due to the intervention (less health care costs due to less complications and less production losses due to less illness) as well as the health gains in terms of life-years gained (LYG), occur only when the pandemic occurs.

The annual and stock renewal costs (including alternative costs) were discounted and summed up to a present value (PV). Likewise, the costs of the AV-drugs, the cost savings due to the intervention and the LYGs were discounted. Since we do not know in which exact year after the stockpiling investment a pandemic would occur, costs, savings and LYGs were calculated as an average of the yearly discounted value during the 30-year time perspective. The net costs and LYG during an outbreak due to intervention are dependent on the perceived risk of an outbreak. The expected cost-effectiveness ratio is calculated as (assuming a risk of a pandemic larger than zero):

$$\frac{\text{PV of purchase and storing costs - risk} \times \text{average PV of net costs if pandemic}}{\text{risk} \times \text{average PV of LYG if pandemic}}$$

In the Netherlands there is no official threshold below which a cost-effectiveness ratio is considered acceptable. However, €20,000 per LYG is often indicated as a possibility for such a threshold. In this paper, we refer to this amount as threshold for acceptable cost-effectiveness and explicitly investigate the expected cost-effectiveness in relation to the threshold and depending on the risk of a pandemic to occur.

Sensitivity analysis

Epidemiological and distributional uncertainties were elaborated in several one-way sensitivity analyses estimating the cost-effectiveness for i) size of pandemic with CAR of 25% and 50% (corresponding to R_0 1.37 and 2.44, respectively (Lugnér et al. 2010)); ii) lower percentage of the population receiving AV-therapy, 60% in stead of the policy goal 80%. In these cases the stock size is adjusted to equal expected number of symptomatic individuals; iii) keeping the stock fixed (sufficient for five million cases) but with a CAR of 25%; iv) using quality-adjusted life years (QALY) gained. The health related quality of life (HRQoL) of patients with influenza treated with oseltamivir (HRQoL weight 0.65) compared to patients receiving placebo (HRQoL weight 0.61) were used (O'Brien et al. 2003). All clinical cases in the non-intervention scenario were assigned a weight of untreated illness (0.61). Non-treated individuals in the intervention scenario were assumed to have less severe illness and assigned the same HRQoL weight as for treated individuals (0.65); v) possibly, there could be two pandemic outbreaks during a time perspective of 30 years. The observed risk of this would be 16% according to the Poisson distribution. Adding an extra refill of the stock (an average of the PV of the purchase cost) in combination with two times higher costs and savings due to a pandemic and a two times extra gain in life-years, illustrates this; vi) the cost of distribution and dispense of the drugs was investigated.

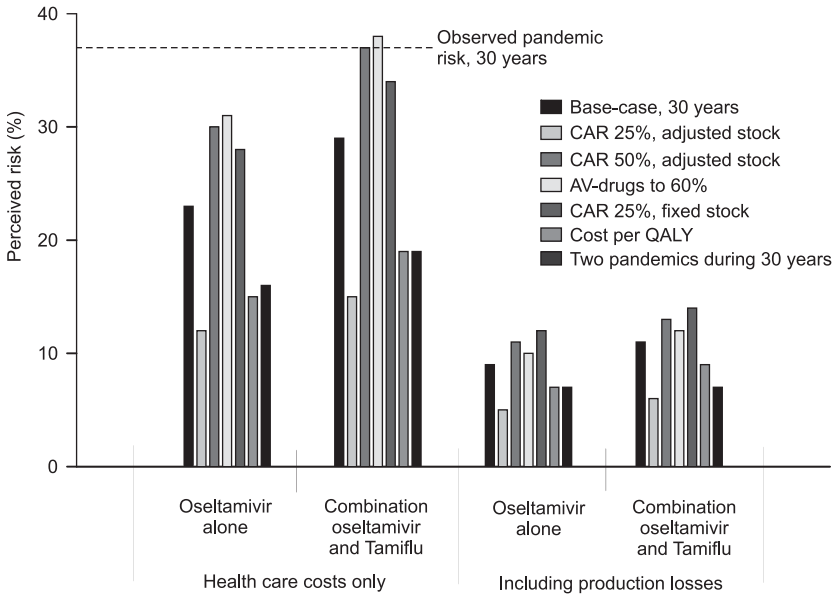

Figure 3.2 Cost-effectiveness ratio €20,000 of stockpiling AV-drugs depending on perceived risk of a pandemic outbreak, base case and sensitivity analyses. Observed risk cut-off point indicated with horizontal line.

RESULTS

Based on the Dutch population (16.6 million people in 2007) there would be 10.4 million infected individuals if a pandemic was left uncontrolled. The policy goal in the Netherlands is that 80% of individuals with symptoms will use AV-drugs, implying that there would be 8.6 million infected cases of which 60% would have symptoms, resulting in about five million individuals receiving AV-drugs.

The stockpiling of oseltamivir alone is cost-effective if the risk of a pandemic influenza outbreak is perceived to be larger than 23% the next 30 years. If the stock is a combination of oseltamivir and Tamiflu®, the perceived risk cut-off point would have to be a little larger (29%). Including production losses shows that the risk would have to be larger than 9% for the oseltamivir alone and 11% for the combination alternative (Figure 3.2). The observed risk that there will be one pandemic during the 30 years is indicated with the horizontal lines in Figure 3.2. This observed risk is higher than the risk cut-off point for the perceived risk. The interpretation is that also with the observed risk, the stock-piling would be cost-effective. The cost-effectiveness ratio for the combination alternative at the observed risk would be around €15,000 per LYG (including productivity losses it is cost-saving).

In the health care perspective there are a couple of cases where stockpiling not necessarily would be cost-effective, as shown in the sensitivity analyses (Figure 3.2). For two cases the cut-off cost-effectiveness point was equal to or higher than the observed risk. If the CAR is as high as 50% (in this case we assumed that the stock would cover to treat all symptomatic cases), and if AV-drugs would only be delivered to 60% of the symptomatic individuals (in stead of 80%), the stockpiling is not cost-effective. Finally, calculations revealed that costs due to distribution and dispense costs could be up to €8 per dose at a cost-effectiveness ratio of €20,000 at a risk of 37%.

DISCUSSION

We show how the cost-effectiveness of stockpiling AV-drugs depends on the risk that there will be an outbreak of a pandemic influenza. At one extreme, if there will be no pandemic it would cost about €177 million to stockpile a combination of AV-drugs during 30 years. On the other extreme, if there for sure would be a pandemic outbreak the stockpiling would be very cost-effective, with a cost-effectiveness ratio beneath €6,000, and cost-saving when including production losses. We further show that the results are sensitive to the size of a pandemic and the proportion that receives the AV-drugs. Is it realistic that 80% of the population will use the drug on time? Is the spread of the pandemic similar to earlier influenza epidemics, or could we expect a higher R_0? Recent estimations about the reproduction ratio based on data from the new influenza A/H1N1 gives various estimates of 2.0-3.2 (Boëlle et al. 2009) and 1.4-1.6 (Fraser et al. 2009) showing the large uncertainty about the actual reproductive ratio in a new outbreak.

The model on which these calculations are based assumes that the virus would continue to be sensitive to the AV therapy. If resistance should develop on a large scale, and no alternative, equally effective and at a similar cost, AV-drug would be available to replace the current this analysis would have to be reconsidered. This strengthens the argument that economic evaluations need to be reassessed when new information is available. Especially, this applies to new or better information about the characteristics of a pandemic virus and effects of a possible vaccine. Furthermore, a recent mathematical model showed that combining different AV-drugs could significantly reduce the resistance of a virus against treatment and the attack rates of the pandemic (Wu et al. 2009). The recommendation to countries already holding a stock of oseltamivir was to include a small stockpile (enough for 1% of population) of a second AV-drug. The costs for this extra stock are suggested to be small (Wu et al. 2009). Using the official price (www.medicijnkosten.nl) to estimate the purchase cost of a stock of zanamivir (another neuraminidase inhibitor) would for the Netherlands cost about €21 million for a one-time purchase. Stockpile these drugs 30 years, assuming a shelf life of five years, including alternative cost, would cost about €90 million (discounted). These rough estimates show that the costs are not likely to be negligible.

As pointed out by Beutels et al. (2008) a health economic analysis is a partial equilibrium model that does not take all opportunity costs of treating symptomatic individuals during a pandemic into account. In case there is a pandemic outbreak of influenza other health care procedures, mainly elective surgery and non-acute treatments, should have to be postponed to free up resources. For a more extensive economic evaluation the disutility of postponing surgery should also be incorporated, measured as number of QALY lost (Beutels et al. 2008). If current contingency plans include postponing of elective surgery it can be questioned if these plans would be changed during a pandemic if resource would become available. The chance that AV therapy would lead to less QALY lost among other than symptomatic patients than if no AV treatment was offered is in our opinion therefore likely to be very small, possibly even negligible. The effects of postponed elective surgery would have little influence on the incremental cost-effectiveness ratio and thus on our specific analysis.

The uncertainties about when and if a pandemic would manifest does not mean that an economic analysis of stockpiling, would that be AV-drugs or a vaccine, is pointless: this analysis anticipate that the cost-effectiveness ratio of stockpiling a combination of AV-drugs falls below the cost-effectiveness cut-off point (including avoided production losses due to treatment), if the risk of a pandemic during a 30-year period is about 11%. Currently, the new influenza A/H1N1 is causing outbreaks around the world, possibly adding another outbreak to the history of documented influenza pandemics. Including this outbreak into the calculus would raise the average annual risk to around 4% (4/100). The resulting observed risk for at least one pandemic during 30 years would be higher (70%).

The beliefs about the risk and spread of a new influenza virus causing a pandemic are very important in the decision whether or not to invest in a stock of AV-drugs or when available, a vaccine.

Chapter 4

Dynamic versus static models in cost-effectiveness analyses of anti-viral drug therapy to mitigate an influenza pandemic

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Health Economics 2010; 19: 518-531

INTRODUCTION

Cost-effectiveness evaluations of health care interventions are often based on models. Such evaluations play an important role for allocating society's scarce resources to meet the public health concerns of preventing disease, prolonging life and promoting health in the whole community (Weinstein et al. 2003). The choice of an appropriate model is crucial to arrive at valid cost-effectiveness ratios (Brennan et al. 2006, Kim & Goldie 2008). Most widely used models are decision tree models and Markov models (Sonnenberg & Beck 1993, Briggs & Sculpher 1998, Bala & Mauskopf 2006). These conventional models implicitly assume that the probability of disease exposure is unaffected by an intervention against it, and therefore the probability of exposure to the disease does not change over time. This assumed constant probability of exposure is realistic for non-transmissible diseases, and can be modeled with so-called static models.

For transmissible infectious diseases the imposed independence between disease exposure and interventions is not realistic and another class of models is required. Interventions against transmissible diseases will not only lower the probability of the treated individual to develop illness, they also lower the exposure of the infection to others. We refer to models that take these non-linear transmission effects over time into account as dynamic models. The non-linearity arises because the probability of a susceptible being infected depends on number of infectious individuals. The best known dynamic model for spread of infection is the SEIR (Susceptible – Exposed – Infectious – Removed) model (Anderson & May 1991, Keeling & Rohani 2008).

Health economists involved in the evaluation of infectious diseases recognize the importance of dynamic modelling (Edmunds et al. 1999, Beutels et al. 2002, Brisson & Edmunds 2003, Drummond et al. 2007). However, a general literature review of cost-effectiveness studies of vaccine programs (Kim & Goldie 2008) as well as disease specific reviews (Beutels 2001, Newall et al. 2007, Anonychuk et al. 2008) reveal that only a minority of the studies on infectious diseases are based on dynamic modelling. One of these reviews presents as a general result that a decision based on cost-effectiveness ratios may depend on model choice (Beutels 2001). Universal influenza vaccination is mentioned as a case where a dynamic model would probably be preferable to a static model; recently, one study showed that vaccination against seasonal influenza was indeed cost-effective when estimated with a dynamic model but not with a static model (Pradas-Velasco et al. 2008).

Dynamic models also play an important role in exploring possible strategies to contain a pandemic outbreak of influenza through controlling transmission (Ferguson et al. 2005, Longini Jr. et al. 2005, Ferguson 2006, Germann et al. 2006, Lipsitch et al. 2007). Since it is doubtful whether there will be an effective vaccine available during a first wave of an influenza pandemic, the proposed strategy in the Netherlands is to treat all individuals suffering from influenza-like illness (ILI) with oseltamivir, an antiviral (AV) drug (Health Council of the Netherlands 2005).

Vaccination and AV therapy affect viral transmission in different ways. With vaccination, virus can only be transmitted by an individual if this individual is exposed and not immunized, either due to incomplete coverage or to an imperfect

vaccine. With AV therapy, virus can be transmitted by any individual after this individual is exposed and before the therapy takes effect. Therapeutic treatment reduces viral transmission only if therapy is started soon after onset of symptoms (Mäkelä et al. 2000, Stiver 2003). This difference has important consequences for the virus transmission dynamics, and it implies that results derived from a dynamic model for a vaccine based intervention do not carry over to results for an AV-drug intervention.

The question is whether a dynamic model would be prefereable to a static model for estimating effects of large scale use of AV-drugs for use in cost-effectiveness analyses (Lynd et al. 2005). To our knowledge, no study has yet used dynamic models that account for the reduced transmission due to AV-drugs in a cost-effectiveness analysis.

This study aims to fill this gap, and more specifically, it aims to examine the differences between the cost-effectiveness ratios of therapeutic AV-drug to mitigate an influenza pandemic as calculated by a dynamic and a static model. Estimates of costs and effects of therapeutic treatment with AV drugs are compared to a non-intervention scenario during a first wave of an influenza pandemic in the Netherlands. The sensitivity of both modeling approaches is assessed for several epidemiologic factors and aspects of drug use.

METHODS

We estimate the cost-effectiveness, expressed as the incremental cost-effectiveness ratio, of therapeutic treatment with AV-drugs compared to non-intervention, resulting in a cost per life-year gained due to the intervention. We do this with one dynamic model and one static model and investigate how the cost-effectiveness ratios differ between these model approaches. In short, the static approach estimates the effects of AV treatment as proportional to assumed number of individuals with ILI during a pandemic. The dynamic approach goes beyond this and estimates the number of individuals with ILI based on characteristics of the virus and the contact structure in the population, and the effect on transmission of AV therapy. The structure of the cost-effectiveness calculations is the same for both approaches (Figure 4.1).

Models

Static model

The static model is a decision tree model. The population is partitioned into six age groups, and each age group is split into low-risk and high-risk groups. The model calculates the health care consumption due to treatment and complications proportionally to the assumed number of infected or symptomatic individuals. This means that there is a specific probability attached to each "chance node" in the decision tree, and the health care consumption depends on number of infected

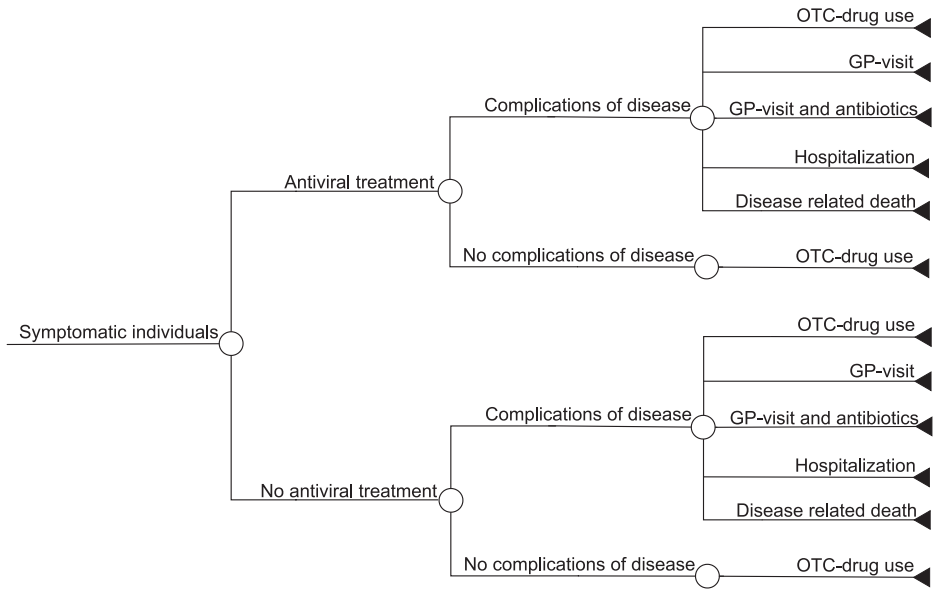

Figure 4.1 Structure for static model and cost-effectiveness calculations

individuals (Figure 4.1). Interventions affect only the treated individual's mortality risk and health care consumption.

Dynamic model

The dynamic model is based on the age-structured SEIR-type of models (Susceptible – Exposed – Infected – Removed). This type of model describes the transmission of the disease, where the compartments represent number of individuals in each state at a certain point in time. Our model includes one additional compartment 'recovering' (G), where individuals still can consume health care due to complications (hospitalizations), but are no longer infectious to other people, and therefore are no longer part of the transmission process (Figure 4.2). Non-symptomatic individuals are also able to spread the virus. The population is partitioned into six age groups and two risk groups (Mylius et al. 2008).

The key epidemiological parameters in the model include the contact rates among and within age groups, the length of the infectious period and the probability of transmission of the virus during a contact. The use of AV-drugs affects the recovery rate and the length of the infectious period.

The cumulative numbers of individuals that enter the various compartments after one pandemic wave were used for the cost-effectiveness calculations. Appendix Chapter 4 shows the model equations.

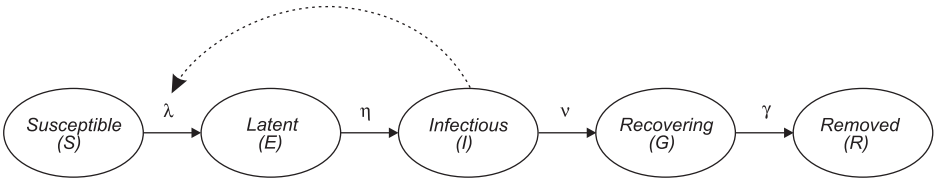

Figure 4.2 Schematic illustration of the dynamic disease model

Note: λ = rate of becoming infected (force of infection), η = rate of becoming infectious, ν = the rate of losing infectiousness, γ = rate of recovery or death (See Appendix Chapter 4 for further details).

Parameterization of the models

At the start of the first pandemic wave, the whole population is at risk of getting infected since we assume that the population lacks immunity against a pandemic virus, i.e. everyone is susceptible. The population size is 16,357,992 people (population of the Netherlands in 2007). Hospitalization and death rates are age and risk-group dependent (Baltussen et al. 1998, Sprenger et al. 1993). High-risk groups include immunocompromised individuals, people with chronic respiratory diseases, and all people older than 65 years in nursing homes.

We assume that 80% of individuals with ILI will use AV-drugs during the first wave*. This assumption is further considered in the sensitivity analysis. Therapeutic treatment is assumed to start within 48 hours of the onset of symptoms. Using antiviral drugs leads to a 50% reduction of health care resource use due to complications, and a 50% reduction in deaths (Stiver 2003, Kaiser et al. 2003). Outpatient health care utilization is based on opinions from an expert panel (Genugten et al. 2003).

The attack rate in an influenza pandemic remains unknown until the epidemic has passed. In the three pandemics during the last century the clinical attack rates (CAR) have been estimated to be around 25-30% (Nguyen-Van-Tam & Hampson 2003). During these three pandemics the CAR has not been evenly distributed over age groups. To facilitate the comparison between the two approaches, we modeled prevalence of ILI in the static model as the overall CAR predicted by our dynamic model (38%) in the base-case scenario.

The transmission is dependent on contacts between susceptible and infected individuals. We use contact patterns between and within age groups derived from self-reported social contact data (Wallinga et al. 2006). The durations of latent and

* Assumption based on estimates from national experts involved in pandemic preparedness.

infectious periods are based on observational data from a Japanese household study (Hirotsu et al. 2004). These are calibrated such that the generation interval (defined as the expected duration between the point in time when one individual is being infected by influenza virus and the point in time when that individual is infecting someone else) matches the observed value of 2.85 days (Wallinga & Lipsitch 2007). A key epidemiological variable is the basic reproduction number, R_0, which describes how many secondary cases of infections are caused by one primary case in a susceptible population (see e.g. Keeling & Rohani 2008, p. 20). The R_0 estimate (1.73) is based on data from the Asian Flu in 1957 (Wallinga et al. 2006). Of all infected individuals, 60% develop clinical symptoms (Jordan Jr. et al. 1958, Fukuda et al. 2004). We further assume that the clinical course of the pandemic virus reflect that of a seasonal influenza virus.

We perform sensitivity analyses to investigate the influence of various parameters. For both models we assume the impact of therapy under the assumptions that 60% and 70% of the population will follow AV-drug treatment (rather than 80% in the base case). For both models we assume different attack rates implying different sizes of the pandemic, expressed as CAR of 25% and 50% (rather than 38% in the base case). These attack rates correspond to a value of R_0 of 1.37 and 2.44, respectively. In addition we provide an alternative comparison between approaches by adjusting the static model using the age-specific attack rates that are predicted by the dynamic model, rather than assuming an overall CAR.

Health care consumption and costs

Health care consumption includes outpatient health care utilization (over the counter drugs, visits to general practitioner (GP) and antibiotic prescriptions due to influenza-related complications), hospitalizations, and costs for therapeutic intervention with AV-drugs. The AV-drugs are distributed through the ordinary health care system. A prescription can be collected at the pharmacy after a telephone consultation with the GP. The societal perspective is taken into account by estimating production losses according to the friction cost method. This is an alternative to the human capital approach to value productivity losses (Brouwer & Koopmanschap 2005, Rothermich & Pathak 1999); our choice is based on the Dutch guidelines for pharmacoeconomic research (Oostenbrink et al. 2004).

We discount life-years by 1.5%, following the Dutch guidelines (CVZ 2006). Costs are not discounted, since these are assumed to arise within one year. Unit costs of direct medical costs and production losses were collected from different sources and expressed in 2005 prices. Assumptions, unit costs for the cost-effectiveness analysis and sources are presented in Appendix Chapter 4.

RESULTS

According to the dynamic model about 10.4 million people of the 16.4 million Dutch inhabitants would be infected during an influenza pandemic of which 6,2 million would have ILI. The pandemic would result in around 9,000 deaths if left uncontrolled. According to the static model, number of deaths would be 1.4 times higher. In both approaches these numbers would be about 40% lower when patients with ILI are treated with AV-drugs. We combined these results with estimates on health care utilization to investigate the cost-effectiveness of AV-drug therapy when estimated with the different model approaches. Both models provided favorable and almost identical incremental cost-effectiveness ratios when including health care costs only: €1,695 (static model) and €1,637 (dynamic model) per life-year gained, and intervention becomes cost-saving when including productivity loss (Table 4.1).

We further investigated the sensitivity of the models to changes in assumptions (Figure 4.3). The impact of a different policy goal was examined through lowering the percentage of the population that would use AV-drugs. With lower use of AV-drugs the difference between the models became bigger. Furthermore, the dynamic model provided a higher cost-effectiveness ratio than the static model when use of AV-drugs was lower than the base assumption of 80%. Evidently, higher use of AV-drugs reduces the transmission, making the estimates approaching each other.

The impact of changing the size of the epidemic, expressed as changing the CAR, did not change the cost-effectiveness ratio in the static model. This is explained by the fact that both costs and effects are proportional to the number of infected individuals, and therefore the ratio of costs and effects remains unaffected by the number of infected individuals. Contrary to this, the cost-effectiveness ratio of the dynamic model was very sensitive to these changes in size. For a CAR of 50% the relation between the ratios from the different models switched, the cost-effectiveness ratio from the dynamic model became higher (€2,556 per life-year gained) than that of the static (€1,695 per life-year gained).

Next, we investigated the impact on the static model of the age-specific attack rates derived from the dynamic model when analyzing the uncontrolled pandemic. The cost-effectiveness ratio calculated with the static model increased to €2,564 per life-year gained and thus became higher than that of the dynamic model. Number of life-years gained between non-intervention en AV therapy now became nearly identical in the two model approaches. The remaining difference between the two ratios is the due effect of reduced transmission (Figure 4.4).

Table 4.1 Results from cost-effectiveness models of therapeutic treatment of pandemic influenza. Costs in thousands € 2005.

	Static model				Dynamic model			
	Non-intervention		Therapeutic antiviral drugs		Non-intervention		Therapeutic antiviral drugs	
	Number	Cost	Number	Cost	Number	Cost	Number	Cost
Infected	-	-	-	-	10369872	-	8594056	-
Influenza like illness	6221923	-	6221923	-	6221923	-	5156433	-
Direct costs								
GP-telephone calls	0	0	4977538	51737	0	0	4125147	42877
Antiviral drugs	0	0	4977538	105026	0	0	4125147	87041
GP-visits due to complications	1555481	32336	933288	19401	1555481	32336	773465	16079
Antibiotics	466644	5968	279987	3580	466644	5968	232040	2968
OTC drugs	4977538	30735	4977538	30735	4977538	30735	4125147	25472
Hospitalization	29256	134389	17553	80634	22941	105384	13851	63625
Total direct costs	-	203428		291114		174422		238061
Effects								
Number of deaths	12362	-	7417	-	9012	-	5362	-
Life years lost	143297	-	85978	-	108309	-	64938	-
Life years lost discounted	129351	-	77610	-	96795	-	57912	-
Production losses								
Due to ILI	-	1208442	-	685172	-	1235487	-	579599
Due to prod reduction	-	1170944	-	43221	-	1214232	-	37238
Due to death	-	3534	-	2120	-	3665	-	2275
Total production losses	-	2382920	-	730513	-	2453384	-	619111
Cost-effectiveness ratio (using incremental direct costs, and discounted life-years gained)		€1695 per life-year gained				€1637 per life-year gained		

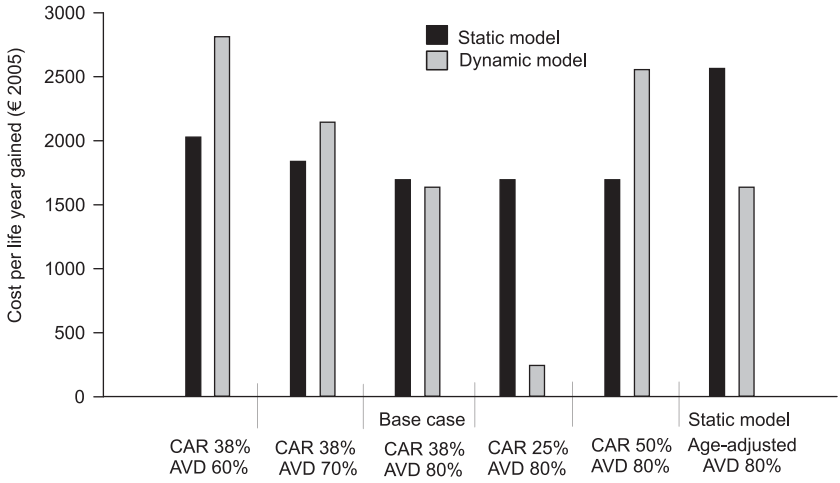

Figure 4.3 Cost-effectiveness ratios of the static and dynamic model for different assumptions about the clinical attack rate (CAR) with 80% of people with influenza-like illness using antiviral drugs, and for different assumptions about the percentage of persons with influenza-like illness using antiviral drugs (AVD)

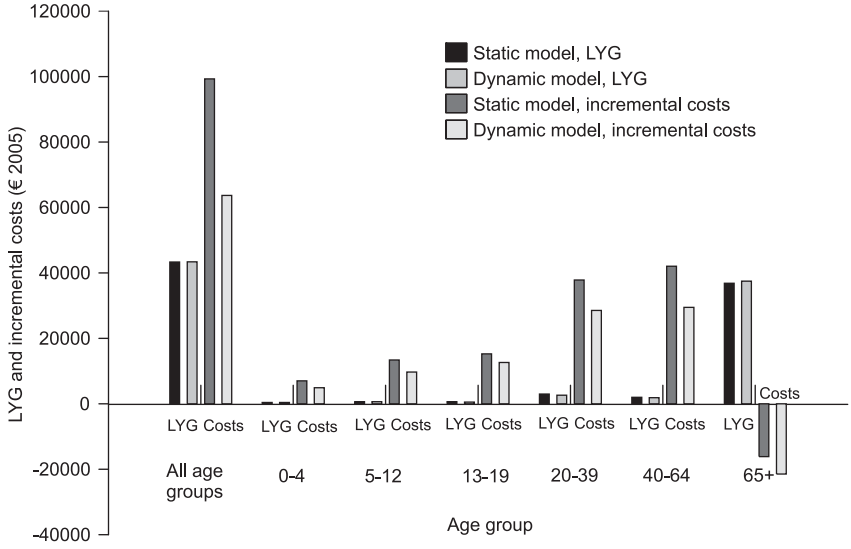

Figure 4.4 Life-years gained (LYG) and incremental costs between AV-therapy and non-intervention, age-adjusted static model and dynamic model. Life-years gained are not discounted in order to show an unbiased picture of the transmission effect.

DISCUSSION

We estimated the epidemic size, health care utilization and costs, as well as production losses of an influenza pandemic with two different models, one dynamic and one static. For both models we evaluated a scenario for an uncontrolled pandemic and an intervention scenario with therapeutic use of AV-drugs in a Dutch setting. We find that therapeutic use of AV-drugs during an influenza pandemic is cost-effective compared to a non-intervention scenario. This result is robust in the sense that it does not depend on the model (static or dynamic) that is used for the estimates, and in the sense that it does not change when less AV-drugs are used than planned, or when attack rates are higher than anticipated. All cost-effectiveness ratios are below the (unofficial) threshold of €20,000 per life-year gained that is often applied in the Netherlands.

It is tempting to assert that the robustness of our finding implies that model choice is unimportant for economic underpinning of pandemic planning. We believe that such an assertion would be misguided. Even though both the static and the dynamic model conclude that the intervention is cost-effective, there are a number of differences between the two model approaches that are crucial in planning for an influenza pandemic. Below we list four key differences.

First, the two modeling approaches do differ in the expected cost-effectiveness ratios for most scenarios. If a different threshold for cost-effectiveness would be applied, the outcome may differ between the models.

Second, the two modeling approaches do differ in their ability to describe how the infection attack rates may change over different age and risk groups. In the static model it is not possible to know the precise distribution of attack rate over various age and risk groups unless the age-stratified attack rate is given a priori for each scenario. In contrast, in the dynamic model the distribution is consistently inferred for each scenario from a single global infection attack rate in the uncontrolled scenario. We have shown that for influenza, where different age and risk groups contribute differently to disease burden and costs, the changing infection attack rates over the groups are extremely important. This finding significantly extends earlier comparisons of modeling approaches to assess the cost-effectiveness of influenza control (Pradas-Velasco et al. 2008).

Third, the two modeling approaches do differ in their sensitivity of the expected cost-effectiveness ratio to changes in infection attack rate. The static model suggests that the cost-effectiveness ratio is insensitive to the infection attack rate, and hence there seems to be no uncertainty about the cost-effectiveness ratio even though there is a large uncertainty about the infection attack rate of a future pandemic. In contrast, the dynamic model suggests that cost-effectiveness ratios are sensitive to the infection attack rate, and hence the large uncertainty about the infection attack rate of a future pandemic implies that we actually cannot be completely certain about the cost-effectiveness ratio.

Fourth, a more general aspect is that the two modeling approaches do differ in their ability to deal with the possibility of eradicating a disease. A welfare economic argument to use dynamic models is provided by Geoffard & Philipson (1997). They

show that the welfare effects of eradication of a disease by means of vaccination only can be investigated by taking the dynamic externalities into account. They argue that the most important welfare effects are the avoided, costly prevention efforts for future generations, an aspect that is not accounted for in a static analysis. For example, the economic benefits of measles eradication in the USA were estimated taking into account a force of infection that decreased over time, even if the model did not describe the actual transmission (Miller et al. 1998). The point is that using a force of infection that changes over time takes us beyond the framework of static models.

To understand the similarities and differences between the static and the dynamic modeling approaches, it is convenient to think of a static model as a specific, albeit unrealistic, case of a dynamic model. This special case arises when the initial proportion of susceptible individuals in each group would be equal to the final infection attack rate in that group, and when all susceptible individuals are infected instantaneously by the first influenza case. The latter condition requires the unrealistic assumption that the reproductive number R_0 would be very high. This argument leads us to expect that a static model performs equally well as a dynamic model if the disease is characterized by a high value for R_0 (Edmunds et al. 1999). We note that this is not the case for pandemic influenza (e.g. Wallinga & Lipsitch 2007); hence we have no guarantee that static and dynamic models for pandemic influenza result in similar outcomes.

Considering the static model as a specific, unrealistic case of an dynamic model with a very high value for the reproductive number, helps to understand that in this case an intervention may reduce the initial proportion of susceptible individuals or may reduce the consequences of infection, but may not reduce the effective reproductive number or the probability of a susceptible being infected. That is, a static model cannot account for a reduced risk of infection for a susceptible individual that results from an intervention aimed at another individual (the so-called herd immunity effect). This has been noticed before. For example, Welte et al. (2005) showed how a static model of chlamydia screening could lead to inefficient conclusions, resulting in targeting wrong groups for screening.

It is tempting to assert that a static model always provides a conservative estimate of the cost-effectiveness since it does not account for herd immunity and therefore underestimates the health effects. However, such an assertion is not always tenable. Brisson & Edmunds (2006) showed that vaccination against varicella-zoster virus in children could cause more disease in older individuals, such that vaccination would result in a loss in QALY. Here we show that for the specific case of mitigating an influenza pandemic using AV-drugs the herd immunity not only impacts the health effects and health care utilization, but also the demand for AV-drugs and related costs.

As in any other scenario study we have made a few simplifying assumptions that should be addressed. Throughout this study we have assumed the effectiveness of AV-drug therapy to remain constant. The effectiveness might decrease if the pandemic influenza virus develops resistance against the antiviral drugs. AV-drug resistance often leads to a loss of transmissibility in the virus, and model studies have shown that the threat of an emerging resistant virus that is less transmissible should

not discourage the use of AV-drugs, at least not at intermediate levels of use (Lipsitch et al. 2007). Throughout this study we have assumed that individual behaviour remains unaffected by the ongoing pandemic. However, pessimistic expectations about an epidemic could also influence people's beliefs about the future epidemic, even leading to more risky behavior (Auld 2003). Individual, voluntary measures such as avoiding public transportation and staying home from work would also influence the transmission (Sadique et al. 2007).

A dynamic model is most useful for prediction of cost-effectiveness of infectious disease control measures, provided that there is sufficient data to parameterize such a model, if interest is in both direct and indirect effects of interventions. If the interest is only in direct effects, for example when we know an intervention has no impact on the transmission of the infectious agent, a static model may suffice. But in general the indirect effect of reduced transmission is a gain, not only for the treated individual, but also for the whole population, providing a significant public health benefit. The non-linear disease dynamics that cause these indirect effects of interventions needs to be recognized (Brandeau et al. 2003). In the specific case of pandemic influenza, we require information on the expected effects and costs of interventions, both the direct and indirect, as well as the sensitivity of these expectations to our assumptions (see e.g. Duintjer Tebbens et al. 2008). Whereas dynamic models make explicit that our estimates for cost-effectiveness depend on the assumed size of an epidemic, static models implicitly assume that the assumed epidemic size is irrelevant. For decisions about an appropriate size of a stockpile of AV-drugs in order to be able to mitigate a pandemic these differences may be vital. We argue that for pandemic preparedness planning static models have a limited use.

APPENDIX CHAPTER 4

The dynamic model

The dynamic model is formulated as a set of ordinary differential equations. The population is divided into six age groups and two risk groups. The frequency of contacts between individuals is dependent on their age groups. The variables $S_{a,r}$, $E_{a,r}$, $I_{a,r}$, $G_{a,r}$ and $R_{a,r}$ denote number of susceptible, latent (or exposed), infectious, recovering and removed (immune or dead, meaning that these individuals cannot re-enter the susceptible compartment) individuals in age/risk group *a,r*. The parameter λ represents rate of becoming infected, η represents the rate of becoming infectious, ν the rate of losing infectiousness, and γ denotes the rate of recovery or death, all measured in days (Table A4.1).

The model equations assume that the durations of exposed and infectious periods follow a realistic gamma distribution (Wearing et al. 2005). Technically, this is accomplished by splitting up both exposed and infectious compartments in n_E and n_I consecutive stages, respectively. The average time spent in each consecutive stage is $1/\eta$ for exposed individuals, and the total exposed period is therefore n_E/η ; the average time spent in each consecutive stage is $1/\nu$ for infectious individuals, and the total infectious period is therefore n_I/ν (Table A4.1).

Values of n_E and n_I,η and ν are chosen such that the generation interval for influenza matches observed averages of 2.85 days (Wallinga & Lipsitch 2007).

Table A4.1 Parameters and their values in the dynamic model

Parameter		Value
n_E/η	Mean exposed period	1.95 day
n_I/ν	Mean infectious period	1.60 day
$1/\gamma$	Mean recovery period	7.00 day

Table A4.2 Normalized age-specific contact matrix C

	0–4	5–12	13–19	20–39	40–64	65+
0–4	1.000	0.186	0.105	0.204	0.094	0.068
5–12	0.186	1.232	0.145	0.157	0.092	0.052
13–19	0.105	0.145	1.549	0.350	0.259	0.103
20–39	0.204	0.157	0.350	0.410	0.268	0.136
40–64	0.094	0.092	0.259	0.268	0.228	0.123
65+	0.068	0.052	0.103	0.136	0.123	0.349

Source: Wallinga et al. (2006)

The differential equations are:

$$\frac{dS_{a,r}}{dt} = -\lambda_{a,r} S_{a,r}$$
$$\frac{dE^{0}_{a,r}}{dt} = \lambda_{a,r} S_{a,r} - \eta E^{(0)}_{a,r}$$
$$\frac{dE^{(i)}_{a,r}}{dt} = \eta E^{i-1}_{a,r} - \eta E^{(i)}_{a,r}$$
$$\frac{dI^{(0)}_{a,r}}{dt} = \eta E^{n_E}_{a,r} - \nu I^{(0)}_{a,r}$$
$$\frac{dI^{(j)}_{a,r}}{dt} = \nu I^{(j-1)}_{a,r} - \nu I^{(j)}_{a,r}$$
$$\frac{dG_{a,r}}{dt} = \nu I^{(n_I)}_{a,r} - \gamma G_{a,r}$$
$$\frac{dR_{a,r}}{dt} = \gamma G_{a,r}$$

where the superscripts i and j ($i \in \{1,\ldots,n_E\}$ and $j \in \{1,\ldots,n_I\}$) denote the stage numbers. The hazard rate for a susceptible individual of becoming infected in age/risk group *a,r* is described by:

$$\lambda_{a,r} = q \sum_{b} c_{a,b} \sum_{s} I_{b,s}$$

where *a* and *b* are age groups and *r* and *s* are risk groups. The parameters $c_{a,b}$ describe the contact rate between individuals in age groups *a* and *b* (Table A4.2). The infectivity parameter *q* was chosen such that $R_0 = 1.73$ (Wallinga et al. 2006).

In the cost-effectiveness calculations we use the cumulative number of infections, hospitalizations and deaths after one pandemic wave as calculated by this model.

Assumptions regarding cost-effectiveness analysis of intervention vs. non-intervention

Both the static and the dynamic model use the same assumptions regarding population structure and health care consumption (Table A4.3). In the cost-effectiveness analysis unit costs and other economic parameters are collected from different sources (Table A4.4).

For productivity loss due to death, the friction cost method counts a friction period after which the person is replaced and the productivity is resumed. This

Table A4.3 Assumptions in the static and dynamic models

		Age groups					
		0-4	5-12	13-19	20-39	40-64	65+
Population	16357992						
Proportion of total population	High risk	0.0014	0.0023	0.0020	0.0162	0.0215	0.0506
	Low risk	0.0577	0.0951	0.0835	0.2478	0.3278	0.0942
Remaining life years[a]		75.79	69.34	62.01	48.10	28.75	10.67
Proportion ILI of infected		0.60	0.60	0.60	0.60	0.60	0.60
Probabilities given ILI							
OTC drugs		0.80	0.80	0.80	0.80	0.80	0.80
GP-visits due to complications		0.25	0.25	0.25	0.25	0.25	0.25
Antibiotics due to complications		0.30	0.30	0.30	0.30	0.30	0.30
Probabilities given infection							
Probability of hospitalization	High risk	$8.70*10^{-3}$	$8.70*10^{-3}$	$8.70*10^{-3}$	$1.29*10^{-2}$	$1.29*10^{-2}$	$3.36*10^{-2}$
	Low risk	$3.45*10^{-5}$	$3.45*10^{-5}$	$3.45*10^{-5}$	$4.31*10^{-5}$	$4.31*10^{-5}$	$5.85*10^{-3}$
Probability of death	High risk	$3.44*10^{-4}$	$3.44*10^{-4}$	$3.44*10^{-4}$	$5.11*10^{-4}$	$5.11*10^{-4}$	$1.69*10^{-2}$
	Low risk	$1.47*10^{-5}$	$1.47*10^{-5}$	$1.47*10^{-5}$	$1.83*10^{-5}$	$1.83*10^{-5}$	$3.21*10^{-3}$

a. average remaining life years in age group
ILI = influenza-like illness

Table A4.4 Unit costs, € 2005

Direct costs		Source
General practitioner visits	20.39	Oostenbrink et al. 2004
Antiviral drugs	15.00	Authors assumption[a]
Antibiotics	6.56	Postma et al. 2005
Over-the-counter drugs	6.06	Postma et al. 2005
Hospitalization, normal care	362.58	Oostenbrink et al. 2004
Intensive care, intensive care	1699.67	Oostenbrink et al. 2004
Number of days in hospital	8	Genugten et al. 2003

a. Assumption based on estimates from national experts involved in pandemic preparedness.

friction period is estimated to 22 weeks during which production is lost. A productivity elasticity of 0.8 is calculated for these losses, meaning that sick leave results in a loss of 80% of the production value (in stead of a proportional 100% loss of production value). The assumptions about the productivity elasticity were originally made in the development of the friction cost method, and are based on Dutch labour market studies (Koopmanschap et al. 1995). The length of the friction period is based on estimated vacancy length in the Netherlands in 2002 (Oostenbrink et al. 2004). The production value is estimated as the average salary among the working population aged 20-64 years, adjusted for participation in the workforce (62% of the population aged 15-64), assuming an eight-hour work day (CBS) (Table A4.5).

Table A4.5 Production losses, assumptions

		Source
Absenteeism due to ILI (days)	1.5	Postma et al. 2005
Reduced productivity due to ILI	50%	Postma et al. 2005
Reduced productivity (days)	3.5	Postma et al. 2005
Absenteeism due to ILI-child age 0-14 years (days)	1.2	Pisu et al. 2005
Working days per year	160	Oostenbrink et al. 2004
Working hours per year	1540	Oostenbrink et al. 2004
Proportion working population of total population (2005)	62.6%	CBS (www.statline.nl)
Average cost per working hour (age 15-64)	€34.15	Oostenbrink et al. 2004

ILI = influenza-like illness

Chapter 5

Mitigation of pandemic influenza: Review of cost-effectiveness studies

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Expert Review of Pharmacoeconomics & Outcomes Research 2009; 9: 547-558

INTRODUCTION

The recent spread of the new influenza A/H1N1 virus (also known as 'swine flu') provides evidence of the continuous threat of an influenza pandemic. This outbreak will possibly add yet another count to the history of pandemics. A pandemic is caused by a, for humans, novel virus, with no or little previous immunity being present in the world population. Another possible threat is the cross-species transmission from flock to humans of the avian influenza A/H5N1 virus, now circulating among wild and domesticated birds. If this virus acquires human-to-human transmission abilities another influenza pandemic could emerge.

The most devastating pandemic documented hit the world in three waves during 1918–19, causing at least 50 million deaths world-wide (Nguyen-Van-Tam & Hampson 2003). Two subsequent pandemics, the Asian flu in 1957-58 and the Hong-Kong flu in 1968-69, had substantially lower case fatality rates (Nguyen-Van-Tam & Hampson 2003).

Dynamic models play an important role in exploring possible strategies to contain a pandemic outbreak of influenza through controlling transmission Longini et al. 2004, Longini et al. 2005, Ferguson et al. 2005, Germann et al. 2006, Lipsitch et al. 2007). Such mathematical models aim to translate individual-level effects of vaccines and antiviral drugs into effectiveness of control strategies. Based on such analyses potentially effective mitigation strategies are proposed. One important component, often missing, in pandemic contingency planning is cost-effectiveness analyses of proposed mitigation strategies. Only scarce economic evaluations of pandemic control are available; even less are done using appropriate dynamic models. This may not be highly surprising, as also for many economic evaluations of seasonal influenza programs the dynamic, nonlinear effects of interventions in infectious diseases are not taken into account (Kim & Goldie 2008). Notably, the development of appropriate dynamic models involves the development of highly complex mathematical structures.

This paper aims to review published studies of pandemic preparedness that include an analysis of economic impact and/or a cost-effectiveness analysis of proposed strategies against an influenza pandemic. We further stress the importance of the use of dynamic models as the sole basis for valid calculations to be derived.

THEORETICAL BACKGROUND

Dynamic models

Since influenza is a communicable infectious disease, dynamic models are most suited to estimate the spread of the disease and the effect on the spread of interventions against transmission and disease. Static models are also used for analyzing cost-effectiveness of infectious diseases' control. However, static models do not take the spread of bacteria or viruses explicitly into account, whereas dynamic models do. In a

static model the clinical attack rate (CAR) – i.e. the percentage of the population having symptoms, in this case influenza - is used to estimate health care resource use and illness related deaths and sickness leave. Dynamic models incorporate indirect effects beyond the index persons targeted by the intervention (for example, reduced spread in the general population through vaccinating a subpopulation). Typically, dynamic models may include herd protection effects and age shifts (Edmunds et al. 1999, Brisson & Edmunds 2003, Brisson & Edmunds 2006). Examples of dynamic models used to describe the spread of infection are the compartmental SEIR model (Susceptible – Exposed – Infectious – Removed) and variants of it (Anderson & May 1991) and stochastic micro-simulation models on the individual level (Longini et al. 2004, Longini et al. 2005). SEIR models can be either deterministic or stochastic. Deterministic models suffice when one can validly assume a large number of infections during all stages of spread, whereas stochastic models are useful when spread is crucially dependent on chance. This is often the case in the beginning of an influenza epidemic or pandemic. In the early stages the spread from the first few cases may either take off or alternatively the spread expires. In stochastic models the parameter values are randomly drawn form a defined distribution, giving different results depending on the specific values in place. Therefore, a number of runs of the model are performed to arrive at an estimated mean with corresponding variation surrounding it. Typically, the results from a stochastic analysis approach the ones from a deterministic model in case of large numbers of infections (Germann et al. 2006). A key epidemiological variable in dynamic modeling of transmittable diseases is the basic reproductive ratio, R_0, which describes how many secondary cases of infections are caused by one primary case in a totally susceptible population (Anderson & May 1991). Generally, an R_0 above 1 indicates that there is a potential for epidemic spread. For influenza, R_0 is typically in the order of magnitude of 1.5-2.5.

Relation between epidemiological and economic models and cost-effectiveness estimations

The outcomes from an epidemiological dynamic model, expressed as numbers of individuals in different stages of disease at specified times, are used as input in an economic decision tree or Markov model (Brennan et al. 2006). Through this linking, estimates of resource use and costs are multiplied with numbers of infections and deceased to calculate the costs during the time period and/or cost-effectiveness of certain interventions. For analyses in the area of influenza this mostly entails that cumulative numbers of individuals that have been infected during the pandemic are estimated with the dynamic model, without and with an intervention. Health care resource use, medical costs and work loss, as well as deaths are subsequently estimated in a decision tree or spread-sheet model for the different scenarios, using straight-forward proportional calculus.

Interventions

Interventions to mitigate a pandemic include vaccination, prophylactic or therapeutic antiviral drug therapy, and non-pharmaceutical interventions. Vaccination not only protects the vaccinated individual against infection but due to a herd protection unvaccinated individuals are also protected if the vaccination coverage is high enough.

However, since there might not be any effective vaccine available at the start of a new pandemic, antiviral drug therapy has long been considered as the option of first choice for treatment and mitigation of an outbreak. Antiviral drug therapy can be given therapeutically when an individual presents symptoms to reduce illness and complications, as prevention to reduce transmission in persons to be exposed and likely to be infected (e.g. health-care professionals) or as post-exposure prophylaxis to persons who have been in contact with ill persons but are not ill themselves (yet). To be able to timely and sufficiently provide the population with these drugs, many countries have invested in stockpiling of these drugs.

Non-pharmaceutical interventions generally refer to various measures of social distancing aiming to reduce contacts between infected and susceptible individuals. These measures typically include closing of schools and travel restrictions.

METHODS

Published literature was searched via PubMed using keywords pandemic, influenza, cost-effectiveness, cost, model, modeling in various combinations. To be included in the review the article would have to be i) original work (no reviews) written in English, ii) including an estimation of only cost or of costs and effects of a human pandemic (not including seasonal influenza epidemics) and, iii) estimating only costs or costs and effects of interventions against a pandemic. Article abstracts were read and evaluated on their appropriateness for the review and 16 articles were read in whole. Of these, 12 articles were judged to adhere to the inclusion criteria i–iii listed above (Balicer et al. 2005, Doyle et al. 2006, Epstein et al. 2007, Hak et al. 2006, Lee et al. 2006, Lugnér et al. 2010, Lugnér & Postma 2009, Medema et al. 2004, Meltzer et al. 1999, Sadique et al. 2008, Sander et al. 2009, Siddiqui & Edmunds 2008) and four were discarded from this review (Beutels et al. 2008, Daems et al. 2005, Ferguson et al. 2006, Nap et al. 2007). With one exception (Meltzer et al. 1999), all reviewed articles were published in 2004 or later. To facilitate the comparisons we re-calculated the costs to 2008 prices using country specific consumer price indices and converted these into euros (€) using the average exchange rate in 2008.

RESULTS

Many of the evaluations are directly or indirectly based on the methodology of the study by Meltzer et al. published in 1999. We note the great impact of that one article on other papers included it in this review, either directly (Balicer et al. 2005, Hak et al. 2006) or indirectly (Doyle et al. 2006, Lee et al. 2006, Lugnér et al. 2010, Lugnér & Postma 2009). The articles were evaluated and compared on various issues, including type of modeling and specific values for health-economic input variables. In particular, we considered what modeling approach was used (dynamic, static and/or decision tree) (Table 5.1). Also, health economic aspects were specified (Tables 5.2 and 5.3). Results on economic impact (without interventions) of a pandemic were compared for those countries where this has been estimated. Furthermore, the costs per health outcome reported in the different studies were reviewed. Finally the cost-effectiveness results, often expressed as cost per life year gained or quality adjusted life year (QALY) gained reported in the studies were highlighted and are discussed.

Modeling approach

Only four of the 12 economic analyses were based on a dynamic transmission model (Epstein et al. 2007, Lugnér et al. 2010, Lugnér & Postma 2009, Sander et al. 2009). Sander et al. (2009) used a stochastic, individual-level microsimulation model to estimate 15 different interventions to mitigate a pandemic in the USA, compared with each other and with a non-intervention scenario. The assumed basic reproductive ratio was 2.0 on average and resulted in a CAR of 50%. The output was put into a decision tree to be able to estimate health-care resource use, costs and life-years gained in different age groups. Next to various pharmaceutical interventions, the effects of school closure during a pandemic (modeled as lasting 26 weeks) were modeled. The model was based on a previously published model (Longini et al. 2004) and applied to the USA health-care and societal setting.

Lugnér et al. (2010) and Lugnér & Postma (2009) used a deterministic SEIR-model to estimate the cost-effectiveness of therapeutic antiviral drug therapy in the Netherlands (Lugnér et al. 2010) and to investigate the cost-effectiveness of stockpiling antiviral drugs (Lugnér & Postma 2009). The age-group specific contacts (6 age-groups) were calibrated so that the efficient contact rates resulted in an R_0 of 1.7. The CAR was estimated at 38% of the Dutch population. Also here, the results were used as input into a decision tree to calculate the cost-effectiveness of therapeutic treatment with antiviral drugs. Furthermore, the results were compared to a static model, using the CAR of 38%. In the base case, the cost-effectiveness ratios were equal, but the static model appeared to be quite insensitive to the CAR. The dynamic model adequately predicted different cost-effectiveness for different CARs and R_0s. These analyses were also based on a previously published model and specifically targeted at to the intervention with antiviral drugs (Mylius et al. 2008). Epstein et al. (2007) investigated the effect of restricting international air traveling on numbers of infected individuals, both worldwide and for the greatest US cities. The model

Table 5.1 Study approaches and basic characteristics

Study (publication year) Country	Topic	Model type	R_0/CAR	Range of case fatality rates
Lugnér et al. (2010) Netherlands	Therapeutic treatment AVD – comparison of modeling approaches	Deterministic SEIR	1.73	0.0000147-0.0169
Lugnér&Postma (2009) Netherlands	Stockpiling AVD	Deterministic SEIR	1.73	0.0000147-0.0169
Sander et al (2009) USA	Different strategies to mitigate pandemic	Stochastic, individual level micro-simulation	2.0	0.025
Epstein et al. (2007) USA	Restricting international air travel	Stochastic SEIR	1.7	n/a
Lugnér et al. (2010) Netherlands	Therapeutic treatment AVD – comparison of modeling approaches	Decision tree	38%	0.0000147-0.0169
Hak et al. (2006) Netherlands	Direct and medical costs due to pandemic	Decision tree	30%	0.038 – 10.8 per 1000
Lee et al. (2006) Singapore	Stockpiling AVD	Decision tree	30%	5 – 1700 per 100000
Siddiqu&Edmunds (2008) UK	Stock-piling AVD and near-patient test	Decision analytic	25%	0.003 - 0.023
Medema et al. (2004) Developed countries	Impact of vaccination with different coverage	Simulation model	35%	1.87%
Meltzer et al. (1999) USA	Vaccination of US population	Monte Carlo simulation	25%	0.024 - 0.42 per 1000
Doyle et al. (2006) France	Intervention strategies (preparedness plan France)	Monte Carlo simulation	25%	0.5% - 2.0%
Balicer et al.(2005) Israel	Stockpiling AVD	Spreadsheet model	25%	0.024 - 4.195 per 1000
Sadique et al. (2008) UK	Cost of school closure	Straightforward calculus	n/a	n/a

R_0 = basic reproductive ratio, AVD = antiviral drug, SEIR = Susceptible, exposed, infectious, removed (compartmental dynamic model), CAR = clinical attack rate. n/a=not applicableDeath rates are age and risk group specific. The lowest and highest values are cited.

consists of a set of stochastic differential equations, specifying the relations between five mutually exclusive classes. In the base case, simulations were done assuming an R_0 at 1.7. In the remaining studies (Balicer et al. 2005, Doyle et al. 2006, Hak et al. 2006, Lee et al. 2006, Medema et al. 2004, Meltzer et al. 1999, Sadique et al. 2008, Siddiqui & Edmunds 2008) the cost-effectiveness calculations were based on static models, e.g. decision trees or similar constructions.

Economic impact of a pandemic

There were three studies found that estimated the costs for the USA. The earliest study by Meltzer et al. (1999) estimated that a pandemic (CAR at 35%) would cost about €160,730 million. These costs are almost 4 times as high as estimated by Sander et al. (2009). In this latter model, costs for an uncontrolled pandemic were estimated at €0.20 million per 1000 population, corresponding to a total of €42,330 million (with a US population of 306,1 million). One contributing factor is that production losses due to deaths are included in the earlier model (Meltzer et al. 1999) whereas these are not included in more recent calculations since these are reflected in the QALYs (Sander et al. 2009).

The third estimate expressed the costs as a percentage of the US GNP (Epstein et al. 2007). According to this model, restricting national and international air travel would cost less than 1% of the US GNP (estimates in 2006) (Epstein et al. 2007). However, benefits of such restrictions were estimated to minimal or even negative, if not combined with a set of other control measures.

The Netherlands, with a population of about 16.4 million is another country for which different estimates are made for the cost of an uncontrolled pandemic. Hak et al. (2006) estimated health care costs due to a pandemic at around €904 million (using Dutch guideline prices for health care services as published in 2004, here inflated to 2008). Lugnér et al. (2010) estimated direct health care costs using one static and one dynamic model for an uncontrolled pandemic to be around €214 million (static model) and €183 million (dynamic model). As in the case for the USA, a static model indeed estimated the costs to be higher than a dynamic model. The more than 4-fold higher costs derived in the first estimate by Hak et al. (2006) is mainly explained by much higher hospitalization rates and unit cost estimates.

One estimate has been published on the economic impact of a pandemic for the UK (population about 59.8 million). Siddiqui & Edmunds (2008) estimated health care costs to be about €164 million in an uncontrolled pandemic. The authors analyzed two options for the uncontrolled epidemic, one assuming a course as in 1918 and one simulating a 1957–1969-like epidemic. Costs were estimated similar in both options, major differences resulted in the projected numbers of deaths at 344,000 and 44,000, respectively. An estimate for Singapore shows that the costs for an uncontrolled pandemic would be around €0.76 billion (Lee et al. 2006) and there would be about 1,105 deaths in a population of about 4.2 million people. Israel has a population of about 6,7 million and the estimated health care costs for an uncontrolled pandemic were estimated to €41.2 million and €389.1 million for the total economy (i.e. including production losses) (Balicer et al. 2005).

Table 5.2 Health economic aspects of reviewed studies

Study (year) Country	Intervention strategies	Outcome	Costs included	Main findings
Meltzer et al. (1999) USA	Vaccination	Net returns to vaccination	Health care costs (GP, hospitalization), vaccination costs Production losses	Vaccinating 20-64 year olds not at high risk groups would give higher net returns than vaccinating all age and risk groups
Balicer et al. (2005) Israel	Therapeutic treatment AVD; Preexposure prophylaxis AVD: - long- and short term	Cost-benefit ratio	Health care costs (GP, AVD, hospitalization) Production losses	Stockpiling is cost-saving when including indirect costs
Sander et al. (2009) USA	Post exposure prophylactic treatment AVD: - Household targeted - Full targeted Therapeutic treatment AVD pre vaccination School closure	Cost per QALY	Health care costs (GP, medication, AVD, vaccination, hospitalization), costs for travel cost and time lost. Production losses	At CAR of 50%, many interventions are cost-saving. In combination with school closure attack rate are reduced to 6% and 4% respectively, but with high costs.
Siddiqui&Edmunds (2008) UK	Therapeutic treatment AVD Test and treat positive cases with AVD	Cost per QALY	Health care costs (GP, hospitalization, AVD, tests) stockpiling costs	Treat only program is cost-effective, Program with prior testing not cost-effective
Lugnér et al. (2010) Netherlands	Therapeutic treatment AVD	Cost per life year gained	Health care (GP, medication, hospitalization, AVD) Production losses	Cost-effective to treat therapeutically with AVD
Lugnér&Postma (2009) Netherlands	Stockpiling AVD for therapeutic treatment	Cost per life year gained	Health care (GP, medication, hospitalization, AVD) Production losses	Cost-effective to stockpile for treating therapeutically
Doyle et al. (2006) France	Vaccination (strain specific); Therapeutic treatment AVD; Prophylactic treatment post exposure Priority population	Cost per avoided event	Medication costs	Vaccinating total population costs the least per avoided case
Medema et al. (2004) Developed countries	Vaccine production method: egg-based or cell culture based	Cost per avoided event	Health care costs (GP, hospitalization), vaccination costs	Cell culture-based vaccine manufacture prevents more influenza cases than egg-based

Lee et al. (2006) Singapore	Prophylactic treatment AVD Therapeutic treatment AVD	Costs and lives saved	Health care (outpatient treatment care, AVD, hospitalization) Production losses	Cost-effective to treat therapeutically with AVD, Maximizing economic benefit: 40% stock-pile, max treatment benefit 60% stock-pile
Hak et al. (2006) Netherlands	None	Health care costs	Health care costs (GP, hospitalization)	Preventive measure that would prevent 50% deaths is cost-effective
Epstein et al. (2007) USA	Restrict air travel	Cost as percentage of GNP	GNP losses	GNP loss due to (passenger) flight restrictions is estimated to be small (1% of GNP)
Sadique et al.(2008) UK	Closing schools	Productivity losses	Production losses for parents caring for child <16 years of age (16.1 % of labour force)	Production losses would be €0.28-169 billion per week.

AVD = antiviral drug, CAR= clinical attack rate, GP=general practitioner, QALY = quality adjusted life-year, GNP = gross national product

Table 5.3 Unit costs € 2008 prices

Cost items	Balicer et al. (2005) Israel	Doyle et al. (2006) France	Hak et al. (2006) Netherlands	Lee et al. (2006) Singapore	Lugnér et al. (2010) Netherlands	Lugnér& Postma (2009) Netherlands	Medema et al. (2004) Developed countries	Meltzer et al. (1999) USA	Sander et al. (2009) USA	Siddiqui& Edmunds (2008) UK
Physician visit	34	-	22	21	21	21	43	290-442	68	48
Medication (antibiotics or non-specified)	-	-	10	-	7	7	-	-	3-6	-
Vaccination	-	6 (dose)	-	-	-	-	20	15	12	-
AVD therapeutic (days or course)	7 (5 days)	10	-	16	16	16	-	-	17	46
AVD prophylactic	5 (7 days)	7 course)	-	12 (week)	-	-	-	-	-	-
Over the counter drugs	-	-	-	-	6	6	-	-	4	-
Hospitalization	236 (day)	-	5811 (episode)	182 (day)	382 (day)	382 (day)	392 (day)	3250-7389 (episode)	2141-824 (episode)	1096 (episode)
Emergency department	-	-	-	-	-	-	-	-	-	117
Intensive care unit	-	-	-	-	1790 (day)	1790 (day)	-	-	-	-
Administration costs	-	-	-	-	-	-	-	5	7 per vaccination	23 (course/ test)
Stockpiling test	-	-	-	-	-	-	-	-	-	1 per test or course
Production losses	53 (day)	-	-	57-88 depending on age	36 (hour)	36 (hour)	-	63- 97 (day)	673 (week)	-

Remarks	Physician visits include prescription drugs and diagnositc tests. Costs disc 3%	2 doses vaccine	Cost per death (€2591): GP specialist first aid diagnositics intensive care general ward ambulance	Number lost days at work depending on severity of disease	AVD 10 days. Costs disc 4%, LYG 1.5%	AVD 10 days Included annual storage and opportunity costs. Disc 4%. Stockpiling base case 30 years	LYG disc 5% Vaccination includes admin costs	Physician visits and hosp include medication and prodloss and vary with age	Hosp cost per diagnosis Prodloss higher for teachers. 2 doses vaccine. 20% added to costs of AVD/ vaccine for distribution and storage	AVD include admin. cost. Stockpiling base case 30 years. Costs and benefits disc 3.5%

Lyg=life years gained, disc=discounted, prodloss=production losses, hosp=hospitalization, admin=administration costs inflated to 2008 using HCPI for European countries (http://epp.eurostat.ec.europa.eu) and CPI calculator for the USA (http://data.bls.gov/cgi-bin/cpicalc.pl). Average exchange rate 2008 is used for expressing other. Two articles [16,23] did not involve unit cost estimates for resource use. currencies in euros (http://www.oanda.com/convert/fxhistory).

Interventions

Antiviral drug treatment and stockpiling

Four of the reviewed articles explicitly estimated the cost-effectiveness of stockpiling antiviral drugs. In general, for the four countries Israel (Balicer et al. 2005), the UK (Siddiqui & Edmunds 2008), Singapore (Lee et al. 2006) and the Netherlands (Lugnér & Postma 2009) the authors conclude that stockpiling is cost-effective if intended to treat symptomatic individuals. It was also indicated that under specific circumstances prophylactic use of stockpiles might also be cost-effective. For example, this was the case if prophylaxis was targeted at persons with a high risk of complications (Balicer et al. 2005). The forth study estimated the cost-effectiveness of stockpiling antiviral drugs for prophylaxis for the USA. This study explicitly aimed to include all costs related to stockpiling and delivery to be reflected in the price of the drugs (Sander et al. 2009). They concluded that targeted antiviral prophylaxis is the most effective single strategy and could potentially be cost saving.

More specifically, Balicer et al. (2005) estimated the benefit-cost ratios of therapeutic use and of prophylaxis of the stockpiled antiviral drugs. If benefits, expressed in monetary units, exceeded the costs for stockpiling and delivery, the intervention was cost-saving. Benefits counted involved avoided health care costs and avoided workdays lost (indirect costs, excluding however indirect costs due to premature death). A number of strategies were investigated, including therapeutic, pre exposure or post exposure prophylactic use for the total population or for high-risk groups only (those with increased risks of complications). Therapeutic use of antiviral drugs for all patients and for high-risk patients only, as well as post exposure prophylaxis (short-term involving 7 days) were all cost-saving when both direct and indirect costs were included. Long-term pre exposure prophylaxis (50 days) was not cost saving, also not when indirect costs were included. The most cost-saving option would be therapeutic treatment of high-risk patients. The recommendation put forward in the article is to consider providing therapeutic treatment to all patients, combined with post exposure prophylaxis to close contacts of patients (Balicer et al. 2005).

Siddiqui & Edmunds (2008) investigated stockpiling of antiviral drugs being used for treatment either without or with near-patient testing for influenza. In the test & treat scenario, individuals with influenza-like illness would only be treated if the test was positive for influenza. Again, the authors investigated two scenarios, one with death rates similar to the pandemics of 1957 and 1968, and one with death rates comparable to the 1918 pandemic. Treatment of illness was cost-effective from the NHS-perspective for both pandemic scenarios according to national cost-effectiveness thresholds, at €19,810 and €2,700 per QALY, respectively. The option to first test all influenza-like illness cases was not deemed to be cost-effective, although one scenario was around GPB 1,000 (€1,400) above the most cited threshold of GBP 30,000 per QALY (€37,800).

One article investigated the cost-effectiveness of stockpiling for prophylaxis in Singapore and shows that the longer the duration of prophylaxis is, the higher cost-effectiveness ratios are (Lee et al. 2006). In particular, costs per life saved increase from €1.20 million for 6 weeks of prophylaxis to €2.40 million for maximum

prophylaxis (24 weeks). Costs per life saved was relevantly reduced if prophylaxis would be targeted at high-risk groups and/or those >65 years. Treatment of symptomatic individuals was shown to be cost saving for all age and risk groups.

The cost-effectiveness of stock piling antiviral drugs in the Netherlands has also been estimated in relation to the risk of a pandemic outbreak (Lugnér & Postma 2009). If the risk of an outbreak is above 9%, keeping and renewing the stock during 30 years would be cost-effective including production losses. If only health care costs are included the risk would have to be about 23-27% for the stock piling investment to be cost-effective. These calculations are based on the estimates in Lugnér et al. (2010), and thus based on the same dynamic model (Mylius et al. 2008). Apart from the costs in that previous study, storing, stock turnover and opportunity costs are added (Lugnér & Postma 2009).

Two articles estimate the cost-effectiveness of antiviral drug therapy, without explicitly including any stockpiling costs (Doyle et al. 2006, Lugnér et al. 2010). Doyle et al. (2006) investigated the French preparedness plan and estimated that therapeutic treatment of the whole population with antiviral drugs would cost €900 per avoided hospitalization and €3,700 per avoided death during two pandemic waves each lasting 10 weeks. The second one concluded that treatment of symptomatic cases would be cost-effective, at an incremental cost-effectiveness ratio of €1,700 per life-year gained (Lugnér et al. 2010).

Vaccination

Meltzer et al. (1999) were the first to publish on the costs and cost-effectiveness of interventions against pandemic influenza. Their aim was specifically to investigate the economic impact of vaccine-based interventions in the USA. As one of the early models, the model was static, without taking the spread of disease explicitly into account. They used age-specific attack rates based on the 1918, 1928-29 and 1957 epidemics and pandemics. The economic impact was measured as the net returns, defined as the value of avoided outcomes (that is, avoided costs) minus the cost of vaccination. The vaccine effectiveness varied between age groups. A high vaccine effectiveness scenario entailed effectiveness of 0.40-0.70 for different health outcomes and health care consumption, where as a low effectiveness vaccine varied between 0.30-0.55. Estimations were made using attack rates between 15% and 35%, analyzed in increments of 5%. With an effective coverage of 40% of the population (and a vaccine price of €21 per dose, including administration costs and costs for treating side effects, one dose per person, high vaccine effectiveness) there would be net savings of vaccination. For higher coverage, only at almost 3-times as high vaccination costs and a relatively low attack rate at 15% net returns were estimated to possibly become negative.

Sander et al. (2009) estimated that a low-efficacy vaccine for 70% of the population would result in 48% less cases and that this would be a less costly strategy than do nothing. The low-efficacy vaccine entails that the efficacy for susceptibility to infection was 0.30 and for infectiousness 0.50. As opposed to the previous study, this result was based on an explicit dynamic model. Compared with no intervention vaccination would save 130 QALY per 1,000 population in the USA. In combination

with closing schools, vaccination would cost about €35,030 per QALY gained compared to full targeted antiviral prophylaxis alone.

Medema et al. (2004) estimated cost-effectiveness of different vaccine production technologies (egg-based vs. cell culture). Using a bit unconventional health-economic terminologies, they estimated various outcomes for the two different vaccine production techniques and for one no-intervention scenario: number of influenza cases, outpatient visits, hospitalizations, deaths, and discounted year per life lost. These estimates are combined with the costs for resources used. Cost-effectiveness was estimated at €4,800 per life-year gained, it remains however unclear which options are compared to arrive at this number.

The cost per avoided influenza case in France was estimated to €90 if there were two doses vaccine per person available for a population of €59.6 million (Doyle et al. 2006). Avoiding one hospitalization (death) would cost €2,100 (€9,000) if vaccination would be considered for the total population (Doyle et al. 2006).

Social distancing

Three articles discusses economic effects of social distancing (Epstein et al. 2007, Sadique et al. 2008, Sander et al. 2009).

For the USA, closing schools are assumed to cost 2.5 days productivity losses per week for parents that need to stay at home (for children <12 years) and 5 days per week for teachers and other professionals (Sander et al. 2009). Schools were assumed to be closed for 26 weeks. The simulations include the effect of reduced transmission. The extra costs would be €1.85 million per 1000 population, achieving a reduced attack rate of 39% in stead of 50% if doing nothing. QALY gained were estimated at 69 per 1,000 population.

Sadique et al. (2008) estimated the costs due to school closure during a pandemic in the UK. Estimates showed that about 16% of the workforce also represents the main care givers and are therefore likely to have absenteeism if children have to stay home. Furthermore, since mostly women were expected to be the main care giver, the health and social work sector would be highly affected due to the high proportion women in these sectors. The costs in the base scenario (mostly women taking care of children under the age of 16) would be around €1.22 million per week. There are no estimates presented on the effect on the transmission of closing the schools.

Epstein et al. (2007) showed that in order to significantly reduce the total number of influenza cases in the whole world, at least 95% of air travel would have to be cancelled. At this level of reductions in travel, the delay of a few weeks in the initial spread of the epidemic may have huge effects on the cumulative numbers of cases. The costs are based on estimations from the effects on travel restrictions after the terrorist attacks of 11 September 2001. Costs for the USA were estimated to €68 – €73 billion per year. Adding impacts on labor, the total of €73 billion would rise further to about €77 billion, costs being about 0.8-0.9% of the USA GNP. The authors label this "far from ruinous" for the US-economy. No costs for the rest of the world economy or countries likely to loose tourism and other productive activities were included.

Transmission and health care utilization models

The four economic evaluations based on dynamic models included in this review (Epstein et al. 2007, Lugnér et al. 2010, Lugnér & Postma 2009, Sander et al. 2009) are based on earlier published transmission models for the specific situations in the USA (Longini et al. 2004) and the Netherlands (Mylius et al. 2008). As such these studies had major impact on developing the methodologies for modeling influenza pandemics and economic consequences, without presenting formal cost-effectiveness estimations. Another study that has had a large impact on both the dynamic model development and the cost-effectiveness calculations for the Netherlands was developed by Genugten et al. (2003). The paper published in Emerging Infectious Diseases investigated the health care needs during a pandemic, but did not include any formal cost-effectiveness calculations (Dhankhar et al. 2009). Notably, Genugten et al. (2003) were the only ones that included pneumococcal vaccination as an explicit strategy to control the impacts of pandemic influenza. Recently, and also in the light of new, more effective, pneumococcal vaccines now being available, this strategy has received renewed interest (Dhankhar et al. 2009). For the comprehensiveness of this review these studies are summarized are in Table 5.4.

DISCUSSION

From this review of published cost-effectiveness studies of interventions to mitigate an influenza pandemic it can be concluded that a lot of interventions have indeed been estimated to be potentially cost-effective. Notably, the dynamic models taking a reduction of transmission explicitly into account provide lower cost-effectiveness ratios than the static decision-tree type of models. In particular, the dynamic type of modeling allows for the indirect effects of herd protection from interventions, for example, vaccination, to be taken into account and further enhance the benefits of these interventions. This implies a greater reduction of health care consumption, illness and deaths due to these reduced transmission potentials in the calculations. Specifically, for the USA and the Netherlands, where both types of models have been used to estimate effects of control measurements, this phenomenon that dynamic models come up with more favorable cost-effectiveness can be seen (Lugnér et al. 2010, Sander et al. 2009).

Stockpiling of antiviral drugs was generally found to be highly cost-effective, for example, if using the stockpile for treatment of symptomatic cases (Balicer et al. 2005, Lee et al. 2006, Lugnér & Postma 2009, Sander et al. 2009). In one specific study, using dynamic modeling (Sander et al. 2009), use of the stockpile in large-scale targeted antiviral prophylaxis was identified as the most effective single strategy providing both QALY gains and cost savings.

The expectation is that a vaccine against the now circulating new influenza A/H1N1 virus will be available shortly. With a very-well matched vaccine and thus highly effective (potentially approaching 100%) and a high coverage, the transmission can be expected to be even more contained than what is assumed in the

Table 5.4 Studies of pandemic influenza mitigation strategies

Study (year) Country	Topic	Model approach	Strategies	Outcome measure	Summary of findings
Mylius et al. (2008) Netherlands	Vaccination strategies	Dynamic SEIR model	Vaccination of high risk-groups or high transmission groups	Number of deaths, hospitalizations and ILI	If vaccination before the peak, target at those groups with high-transmission potentials
Longini et al. (2004) USA	Prophylaxis AVD compared with vaccination	Discrete-time stochastic simulation	Targeted prophylaxis AVD to identified contacts, vaccination before influenza season	Number of influenza cases	Targeted prophylaxis has significant effects on slowing spread of influenza, 80 % prophylaxis for 6-8 weeks is almost as effective as vaccinating the entire population
Genugten et al. (2003) Netherlands	Vaccination and AVD strategies, scenario approach	Decision model (static)	Vaccination of risk-groups or total population, pneumococcal vaccination high risk groups, AVD therapy	Hospitalizations and deaths prevented	Vaccination prevents highest number of hospitalizations and deaths

SEIR = Suseptible – Exposed – Infectious – Removed (compartemental dynamic model)

models reviewed here. This of course assumes a high compliance to a national vaccination program. These models where often developed with the threat of an avian influenza virus, with no highly effective vaccination was expected to be available before the peak of the epidemic (for example, 30% was used for a badly matching vaccine). In light of the new influenza A/H1N1 virus these models may thus underestimate the effect of vaccination and subsequently the cost-effectiveness of this intervention. Notably, these models are based on previous pandemics and characteristics of seasonal influenza. The novel influenza has until now showed a slightly different attack rate; in particular, children and young adults seem to be the most vulnerable groups for the infection (ECDC 2009) whereas a seasonal influenza normally attacks older age groups harder, with higher probabilities for complications.

One study linked the closing of schools explicitly to reduced transmission (Sander et al. 2009). Even with the very long closing time assumed (i.e. during the whole of the pandemic period of 26 weeks) the cost per QALY gained is reasonable, illustrating the huge effect of the reduced transmission. A more specific policy would be to close schools for a much shorter period somewhere before the peak of the pandemic. That would reduce the costs substantially but the effect on transmission would probably be almost as high, since school children contribute the most to the spread, especially before the peak (Mylius et al. 2008). Of course, re-opening the schools should not result in a resurgence of the pandemic and merely cause the initial peak to shift rather than to decline or even disappear.

The recent pandemic alert issued by the WHO did not include any recommendations to restrict international travel. The effect in reduced transmission of such a restriction is relatively small, whereas the high costs due to less world trade and tourism is substantial. Moreover, at this stage of the A/H1N1 pandemic morbidity and mortality caused by the virus seems still relatively mild. Most models included in this review assume case fatality rates similar to seasonal influenza, but a few of them presents sensitivity analyses using higher rates based on the devastating 1918–1919 Spanish Flu (Balicer et al. 2005, Meltzer et al. 1999, Siddiqui & Edmunds 2008).

We conclude that the choice of an appropriate model is crucial to arrive at valid cost-effectiveness ratios (Brennan et al. 2006). Health economists involved in the evaluation of infectious diseases recognize the importance of dynamic modelling (Edmunds et al. 1999, Brisson & Edmunds 2003, Beutels et al. 2002, Drummond et al. 2007). However, a general literature review of cost-effectiveness studies of vaccine programs (Kim & Goldie 2008) as well as disease-specific reviews (Beutels 2001, Anonychuk et al. 2008, Newall et al. 2007, Lynd et al. 2005) reveal that only a minority of the economic evaluations of infectious diseases' control is based on dynamic modeling. In this review, the same appears to hold true for cost-effectiveness analyses in pandemic influenza control. To further enhance validity of the approaches, we recommend that further research is directed towards linking dynamic epidemiological models for pandemic spread with economic outcomes, considering the full impacts on national economies inclusive direct, indirect, medical and non-medical costs.

Chapter 6

A cost-utility analysis of antenatal screening to prevent congenital rubella syndrome

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Epidemiology and Infection 2010; 138: 1172-1184

INTRODUCTION

The National Immunization Program (NIP) in the Netherlands is an effective program with a national vaccination coverage rate of about 95% (Lier et al. 2008), inducing a high level of immunization protecting the population against outbreaks of infectious diseases. Through the voluntary and free-of-charge NIP, infants and young children are currently offered vaccination against diphtheria, pertussis, tetanus, poliomyelitis, haemophilus influenzae type B, mumps, measles, rubella, pneumococcal disease, meningococcal group C disease and hepatitis B (risk groups only). Most of these infectious diseases have become very rare in the Netherlands. However, outbreaks of poliomyelitis in 1992–1993 (Oostvogel et al. 2001), measles in 1999-2000 (Hof et al. 2001), rubella in 2004–2005 (Hahné et al. 2009) and mumps in 2007 (Karagiannis et al. 2008) have occurred in low vaccination coverage regions (LVR). In these regions, part of the population rejects participation in the NIP for religious reasons, and as a result some infectious diseases have not been eliminated yet. These regions represent an important obstacle in the otherwise successful control of vaccine preventable infectious diseases in the Netherlands.

Rubella vaccination for girls aged 11 years was introduced in the NIP in 1974. In 1987, it was replaced by universal vaccination using a mumps-measles-rubella (MMR) combination vaccine offered at 14 months and 9 years of age. Even though rubella is a mild infection in children, vaccination is of great public health importance since infection during pregnancy can lead to miscarriage and the congenital rubella syndrome (CRS) (Banatvala & Brown 2004). The risk of complications is highest when the woman is infected during the first half of the pregnancy (Banatvala & Brown 2004). Screening for absence of rubella antigens provides a possibility to offer post partum vaccination against rubella to women who lack protection, i.e. present a negative serology test (sero-negative). Post partum vaccination would protect the foetus in a subsequent pregnancy. Vaccination during pregnancy with the live attenuated vaccine is not advisable, although no complications have been reported in inadvertently vaccinated pregnant women (Banatvala & Brown 2004).

Immigrant women originating from a non-western country may represent another possible risk group in the event of an epidemic in the Netherlands; in several studies the seroprevalence of rubella was found to be lower in this group compared to pregnant women in the general Dutch population (Buiker & Schout 1987, Cornel 2005, Elsacker et al. 2004, Haas et al. 1999, Knoppers 2005, Tjon A Loi et al. 2001, Zwan et al. 1992, personal communication L. Mollema).

All pregnant women in the Netherlands are offered antenatal screening for hepatitis B, HIV, syphilis, rhesus-D factor, irregular antibodies, haemoglobin status and determination of blood group. Screening for rubella antibodies has been recommended for immigrant women and women living in LVR (Elsacker et al. 2004). However, this recommendation was not supported by an economic evaluation and rubella screening was not included in the antenatal screening program, thus it is not standard practice in routine midwifery. In contrast, antenatal screening for rubella antibodies is routinely carried out in other European countries, including Germany (Best & Enders 2007) and France (Lévy-Bruhl et al. 2004),

whereas in Italy (Ciofi degli Atti et al. 2004) and the UK (Best & Enders 2007) it is recommended. A successful screening and post-partum vaccination program may help to prevent rubella during pregnancy, reducing the risk of babies being born with CRS. The cost-effectiveness of such a program is one component of an evidence-based decision and provides important input in public health policy.

This study presents a cost-utility analysis of a screening and vaccination program for rubella in pregnant women in the Netherlands, using recent data from the outbreak in 2004–2005. We analyse three different scenarios: 1) screening non-vaccinated pregnant women in LVR; 2) screening all pregnant women in LVR; and 3) screening non-vaccinated pregnant women in all of the Netherlands.

METHODS

We estimated cost-utility ratios of screening pregnant women for rubella antibodies, with subsequent post partum vaccination of sero-negative women to avoid rubella in later pregnancies. All infants born with one or more defect (defects of the central nervous system (CNS), hearing defect, heart defect) from women with laboratory confirmed rubella infection during pregnancy observed during the 2004-2005 epidemic in the Netherlands were included, together with two cases of foetal death due to rubella infection* (Hahné et al. 2009).

The cost for a screening and vaccination program was weighted against health care costs saved and quality-adjusted life years (QALYs) gained by prevention of rubella infection in pregnancy. If one scenario turned out to be more costly but also more effective in terms of QALYs gained, an incremental cost-utility ratio was calculated, dividing incremental costs by incremental QALYs gained. The resulting ratio shows the cost per extra QALY gained if a more effective, but more costly scenario was chosen. Costs were discounted using a rate of 4% and life-years gained using a rate of 1.5% in accordance with the Dutch guidelines for pharmacoeconomic research (CVZ 2006). The analyses were made from a health-care related costs perspective. Costs were expressed in euro (€), price level 2007.

* The WHO clinical case definition of congenital rubella syndrome (CRS) (Robertson et al. 2003) entails two or more of the following complications in an infant: cataract(s), congenital glaucoma, congenital heart disease, loss of hearing, pigmentary retinopathy. Furthermore, a is case defined if one of the above complications is seen in combination with purpura, splenomegaly, microcephaly, mental retardation, meningocephalitis, radiolucent bone disease, or jaundice that begins within 24 hours after birth. In this analysis we thus deviated from this definition of an CRS.

Scenarios

The three scenarios consisted each of sub-groups representing different groups of women with distinct characteristics regarding rubella status and willingness to accept screening and vaccination. These characteristics determine the number of screenings offered, the costs of screening and vaccination, as well as the number of preventable complications of rubella in pregnancy.

We investigated three possible scenarios for screening: (1) screening all non-vaccinated pregnant women in the LVR (Non-vaccinated LVR) (2) screening all pregnant women in the LVR (all LVR); and (3) screening all non-vaccinated pregnant women in the Netherlands, including pregnant, first generation, non-western immigrant women (non-vaccinated NL). We defined LVR as municipalities where more than 5 per cent of the voters voted for the 'Staatkundig Gereformeerde Partij' (SGP) in the 2006 elections using information retrieved from national statistics (www.verkeizingsuitslagen.nl) (Figure 6.1A). SGP is an orthodox Calvinist political party that bases its point of view on the bible and represents orthodox protestant groups including some who refrain from vaccination. Following this criteria, 60 of the about 460 Dutch municipalities met the definition of a LVR. The reason for choosing this criteria and not, for instance, municipalities with the highest proportion of unvaccinated individuals, was that epidemics of vaccine preventable diseases in the Netherlands are often largely confined to orthodox protestant communities, which are not protected by herd immunity of the general Dutch population due to their social and geographical clustering. In general, municipalities with low vaccination coverage overlap with those with a high percentage of religious voters.

The 2004-2005 epidemic

During the epidemic there were 32 pregnant women notified with rubella infection (Hahné et al. 2009). Thirty-one of these women were living in LVR, one was living outside these regions. All women belonged to a group who were not vaccinated on religious grounds (Figure 6.1B). Of these 32 women, two suffered spontaneous abortions and eleven infants were born with defects associated with congenital rubella. Of 25 women with known parity, for 44% (11 women) it was not their first pregnancy.

Time perspective of the economic analysis

By means of a screening and vaccination program rubella complications could be averted in the event of an epidemic, and to a lesser degree, in the years between epidemics. The probability of an outbreak occurring is, however, difficult to predict. The two most recent rubella outbreaks in the Netherlands occurred within an eight-year interval. We used this to form an assumption about the frequency of outbreaks and thus estimated the cost-effectiveness of a screening and vaccination program (beginning in year 0) for a time span of 16 years during which a rubella outbreak occurred twice, during years 7 and 15, respectively.

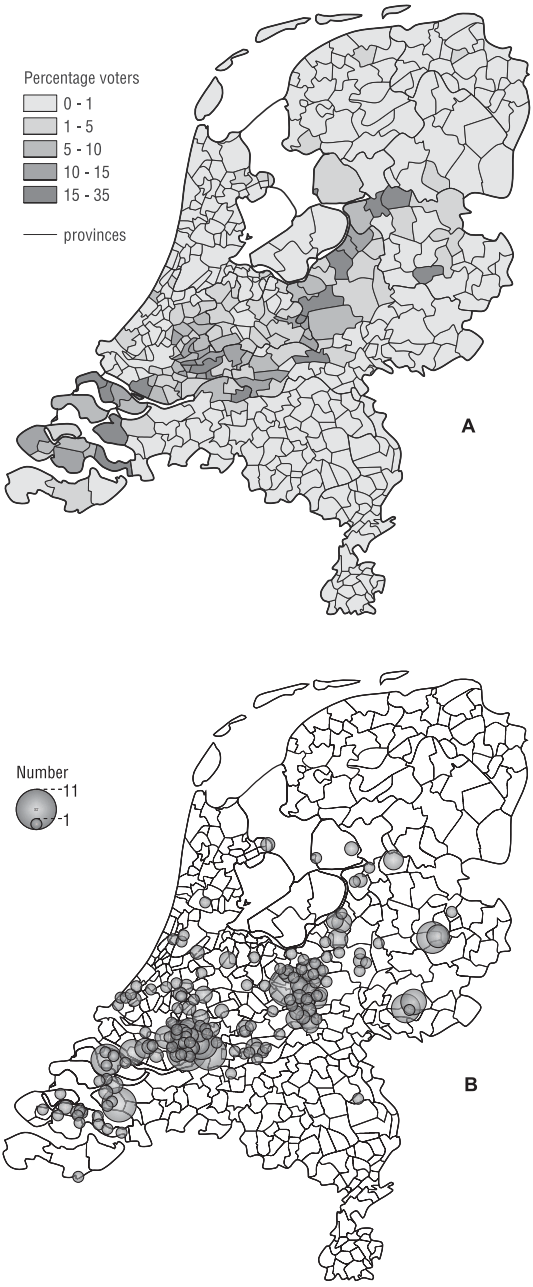

Figure 6.1 (A) Geographical representation of voters on Ortodox Reformed party (SGP) in 2006. (B) Geographical dispersion of rubella infection in the Netherlands, epidemic 2004-2005.

Note: There was statistically significant positive relation between the proportion of SGP votes and number of rubella cases (over-dispersed Poisson regression). For the results from the regression analysis, see Appendix Chapter 6, Table A6.5.

Not all complications occurring during an epidemic or non-epidemic year would, however, be prevented if screening and vaccination were offered. The willingness to accept screening and vaccination, which differs per target group, together with the effect of screening and vaccine efficacy, partly explains why not all rubella complications would be prevented. Furthermore, since pre-conception advice or screening is not regularly provided, rubella complications in a first pregnancy would also not be prevented. The number of prevented complications in a non-epidemic year was adjusted for the probability that a complication would arise in the target group and the chance that a pregnant woman belongs to that specific target group.

Screening program

The cost of a screening and vaccination program depends on the number of eligible women, i.e., number of (non-vaccinated) pregnant women and their willingness to accept screening and/or vaccination. The percentage of non-vaccinated women in each scenario was estimated as 1 minus the average vaccination coverage for the second dose of MMR based on the 1994 birth cohort. In the municipalities included in the LVR, vaccination coverage was on average 90.2%, while outside the LVR it was on average 98.7%, resulting in 9.8% and 1.3% non-vaccinated women in the respective target groups (Lier et al. 2008). It was further assumed that all first generation non-western immigrant women were not vaccinated. The number of pregnant women that would be offered screening in the different (sub)groups was estimated as the number of live born infants multiplied by the percentage of women for whom it was the first pregnancy, using information gathered from national statistics (CBS, website) (Table 6.1). In addition, we included 20% of first generation immigrant women who were on at least their 2nd pregnancy (CBS, website). This was based on the assumption that the first pregnancy of 80% of these women had been handled in the Netherlands, therefore these women would have already been offered participation in the program (Table 6.1).

In general, only women experiencing their first pregnancy were included, as it was assumed that a woman expecting her next child would have already been offered and accepted or rejected screening and vaccination (assuming no women changed their mind after rejecting vaccination the first time). This was done in order to avoid double counting screening costs in a program that continues for several years.

Costs of program

Program costs comprise the cost of the screening test and honorarium, together with MMR-vaccination for sero-negative women who accept post partum vaccination. Since the screening would take place alongside the antenatal health care visits at 12 weeks gestation, the standard blood sample drawn during this visit would also be used for the rubella screening, therefore no extra costs for such a visit were included:

Table 6.1 Number of screenings offered and accepted, and number of accepted vaccinations, per sub-group and total per scenario, (willingness to accept screening is 95% in all groups)

Sub-groups: pregnant women Total per scenario	Number of pregnant women	1st pregnancy +20% of 2nd pregnancy in immigrant women	Number of screenings offered	Number of accepted screenings	Percentage sero-negatieve	Willingness to vaccinate[d]	Number of accepted vaccinations
	Column A	Column B	Column C =A×B	Column D =C×0.95	Column E	Column F	Column G =D×E×F
Non-vaccinated native; LVR	1595	0.386	616	585	11.0%[a]	20%[a]	13
First generation non-west immigrants; LVR	842	0.483 +0.314*20%	460	437	6.2%[b]	90%	24
Total: Non-vaccinated LVR				1022			37
Non-vaccinated native; LVR	1595	0.386	616	585	11.0%[a]	20%[a]	13
Vaccinated; LVR	14679	0.452	6635	6303	2.1%[c]	90%	119
First generation non-west immigrants; LVR	842	0.483 +0.314*20%	460	437	6.2%[b]	90%	24
Total: All LVR				7325			156
Non-vaccinated native; rest of NL	1889	0.452	854	811	2.1%[c]	90%	45
Non-vaccinated native; LVR	1595	0.386	616	585	11.0%[a]	20%[a]	13
First generation non-west immigrants; NL	25506	0.483 +0.314*20%	13921	13225	6.2%[b]	90%	250
Total: Non vaccinated NL				14621			308

a. Seroprevalence 11% (95% CI 6-19) (Ruijs et al. 2009).
b. Seroprevalence in pregnant women participating in the "Amsterdam Born children and their Development" (ABCD) study (personal communication, L. Mollema)
c. Assuming same sero-prevalence among non-vaccinated population in whole of the Netherlands as among vaccinated in LVR (97.9 (95% CI 96.9-98.8) (Haas et al. 1999).
d. Assumed the same for all groups except non-vaccinated women in LVR.,which is based on preliminary results, later published in (Ruijs et al. 2009) (results in (Ruijs et al. 2009) were 17% (95% CI 2-48). The impact of the willingness to vaccinate is investigated in the sensitivity analysis

Screening costs = number of screenings offered × willingness to screen (%)× unit cost per screening [1]

We assumed that the vaccination would take place during a visit to the general practitioner (GP) and included costs for one such visit. Costs for vaccination were:

Vaccination costs = number of sero-negative women × willingness to vaccinate (%) × (vaccine cost + cost of one GP-visit) [2]

The estimated number of screenings offered and sero-negative women can be found in Table 6.1 and unit costs are described in the Appendix Chapter 6.

QALYs gained

A QALY is a combination of a (health-related) quality of life (QoL) weight for a specific health state and the duration of time spent in that health state. Congenital rubella-associated defects are assumed to be permanent, that is, the duration of time spent in that state is equivalent to the expected life years remaining after birth. QoL weights were taken from non-age-weighted disability weights using the formula:

QoL weight = 1- disability weight [3]

The disability weights adopted were derived from disability-adjusted life years (DALYs) calculated for the Dutch population (Melse et al. 2000). Although based on different methodologies, under the assumptions made here (non-age-weighted and life-long inferior health states) the QALY and DALY approaches are similar (Sassi 2006). The QALYs lost due to congenital rubella complications were estimated as:

QALY lost = (life expectancy at birth for a healthy child × QoL weight for a healthy person) – (life expectancy at birth for a child with the specific health state × health state specific QoL weight) [4]

QALYs lost due to complications were estimated as a weighted average based on the outbreak in 2004-2005 and a QoL weight for a healthy infant of one. QALYs lost due to rubella-associated foetal death were calculated as a loss of an entire life, using life expectance at birth in 2005 (78.8 years) and a discount rate of 1.5% (resulting in 46.2 years). Potentially prevented complications in an epidemic were estimated for each subgroup as:

Number preventable complications = willingness to screen (%) × willingness to vaccinate (%) × vaccine effectiveness (%) × number of infants with complications × complications in 2nd or later pregnancy (%) [5]

These calculations formed the base for the potentially gained QALY, estimated as average QALYs lost times number of preventable cases (used in Tables 6.2 and Appendix Chapter 6 Table A6.4), as well as costs saved. Further details are found in the Appendix Chapter 6.

Saved costs

Health care costs were calculated as costs per defect summed by the number of defects. The weighted average of the costs for the different defects seen in the epidemic was used as an estimate of costs saved by averting a complication (excluding health care costs directly related to foetal death). We included five years of saved costs in the base analysis. This is a conservative assumption about cost-savings. Based on data from an online database describing cost-of-illness for different diagnoses in the Netherlands, we assumed 45% of costs for congenital complications occur during the first five years of life (RIVM, kosten van ziekten). Further details about these calculations are found in Appendix Chapter 6.

Non-epidemic years

In non-epidemic years, additional costs could be saved and QALYs gained. We assumed that one case of rubella infection in a pregnant woman occurs in each non-epidemic year in the Netherlands, with a probability that 1 in 3 infections would have led to complications (Hof et al. 2004). It was assumed that 25% of these cases occurred in the native Dutch population and 75% in the immigrant population. This assumption was based on different (informal) sources including surveillance data (Hof et al. 2004).

Sensitivity analyses

Sensitivity analyses (one-way) were performed for the following parameters: willingness to vaccinate, no occurrence of an epidemic within the defined 16 year period, one (instead of 1/3) rubella complications prevented in the inter-epidemic period, less than 44% of women expecting their second child, post-partum vaccination without antenatal screening, foetal death excluded as a complication of rubella infection, expected remaining life-years 25% lower for a child born with complications and life-long treatment costs for children with complications.

RESULTS

The number of preventable congenital rubella complications for each scenario is presented in Table 6.2 together with the potential number of QALYs gained due to the screening and vaccination program. Preventing a complication of rubella infection during pregnancy would lead to an average of 22.9 QALYs gained

Table 6.2 Number of identified infected women and number of preventable complications per scenario

Scenario	Description	Number infected pregnant women	Number complications (including spontaneous abortions)	Number preventable complications[a]	
				Epidemic year	Non-epidemic year
1	Non-vaccinated LVR	31	12	0.953	0.0060
2	All LVR	31	12	0.953	0.0072
3	Non-vaccinated NL	32	13	1.032	0.0955

a. Calculated using equation 5 (epidemic year) and from Table A6.4 (non-epidemic year).

(Appendix Chapter 6 Table A6.2). The costs for the screening and vaccination program are a direct consequence of the number of screenings accepted, proportion of sero-negative women and number of vaccinations accepted (Table 6.1). The yearly expected costs of a screening program are €17,900, €107,800 and €266,600, for scenario 1, 2 and 3 respectively. Scenario 1 'Non-vaccinated LVR' entails the smallest number of eligible women. Scenario 2 'All LVR' is an extension of the first scenario and Scenario 3 'Non-vaccinated NL' involves screening the largest number of women.

The screening and vaccination program during the 16 year period would be cost-effective if targeted at non-vaccinated women in the LVR (€1,100 per QALY gained) (Table 6.3), if judged by an unofficial but often quoted limit of €20,000 for preventive interventions in the Netherlands. Based on the same limit, the other two scenarios would not be cost-effective.

Calculating the incremental cost-effectiveness ratio of the extra gain in QALYs by implementing scenario 3 instead of scenario 1, that is including all non-vaccinated pregnant women in the Netherlands instead of only non-vaccinated women in LVR, it would cost €97,700 per QALY gained.

We further performed a number of sensitivity analyses for Scenario 1, changing some of the assumptions made in the base-case analysis (Figure 6.2). In two of the sensitivity analyses the favourable cost-effectiveness ratio became unfavourable: i) if willingness to accept vaccination by native women in the LVR would be zero (€112,000 per QALY gained) and ii) if there would be no epidemic during the 16-year period (€105,000 per QALY gained). Further calculations showed that the cost-effectiveness ratio in Scenario 1 was below the cost-effectiveness limit when the willingness to vaccinate was above four percent. This means that if less that four percent of the non-vaccinated sero-negative women would accept vaccination, Scenario 1 would not be cost-effective. Post-partum vaccination without screening, whereby all women would be vaccinated regardless of serological status, would also be cost-effective for non-vaccinated women in the LVR (€17,000 per QALY gained). If

Table 6.3 Costs and cost-effectiveness ratios per scenario (€ price level 2007), costs discounted 4%, life-years gained 1.5%

	Yearly cost and QALY gained					Costs and QALY gained over 16 years			
		Non-epidemic year		Epidemic year					
Description	Screening & vaccination[a]	Savings[b]	QALY gained[b]	Savings[c]	QALY gained[c]	Screening & vaccination	Savings	QALY gained	Cost-effectiveness (Net cost[d]/QALY gained)
1. Non-vaccinated LVR	17889	938	0.14	124632	22	216790	174049	39	1100
2. All LVR	107752	1122	0.16	124632	22	1305777	176037	39	28800
3. Non-vaccinated NL	266601	14989	2.19	137095	24	3230772	350555	68	42400

a. Equation 1+ Equation 2. Number of screenings and vaccinations per target group is found in Table 6.1, unit costs in Table A6.1.
b. From Table A6.4.
c. Number preventable complications in epidemic (Equation 5) × average cost and average QALY lost per complication, respectively (Tables A6.2 & 3).
d. Net cost = Screening & vaccination costs - savings

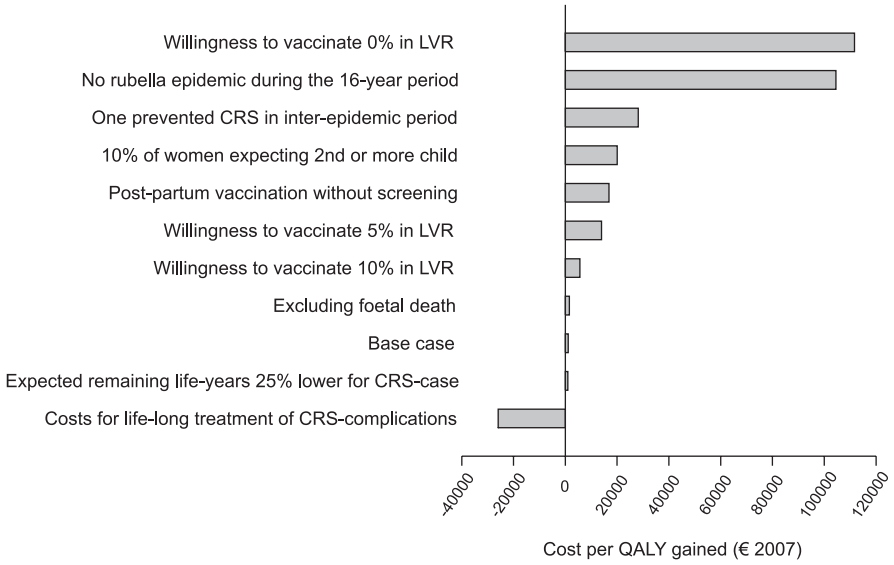

Figure 6.2 Sensitivity analysis of Scenario 1 (non-vaccinated women in LVR)

the remaining life expectancy was lower for an infant born with rubella complications or if the probability of preventing complications would be one in a non-epidemic year, the cost-effectiveness would be more favourable than in the base case. If less than 10% of women were on at least their second pregnancy it would not be cost-effective to screen according to Scenario 1 (€20,100 per QALY gained). If both costs and life-years gained were discounted with the same rate (4%) the cost-effectiveness ratio would change to €2,100 per QALY gained.

For the other two scenarios changing these assumptions influenced the cost-effectiveness of a few analyses. When calculating life-long (up to 77 years, age-adjusted) health care costs for treatment of congenital-complications (i.e. CNS and heart defects), instead of the conservative assumption of five years, Scenario 1 would be cost-saving and Scenarios 2 and 3 would be cost-effective. Costs for hearing disabilities above the age of 5 were excluded in the life-long costs since available cost estimates were not related to congenital defects. Assuming that the rubella infection occurring in a pregnant woman in a non-epidemic year always led to an infant born with complications (instead of a chance of 1/3) then scenarios 2 and 3 would have an cost-effectiveness ratio between €26,900 and €28,100 per QALY gained. Not discounting costs and effects led to lower cost-effectiveness ratios. As a consequence the cost-effectiveness ratio in scenario 2 fell below the threshold (€18,600 per QALY gained). The undiscounted ratio would be €28,300 per QALY gained for scenario 3.

DISCUSSION

Screening pregnant women for rubella antibodies in order to offer post-partum vaccination to sero-negative women is cost-effective if targeted at unvaccinated women in the LVR in the Netherlands. We also investigated the cost-effectiveness of a screening and vaccination program for two other scenarios: including all pregnant women in the LVR regardless of vaccination status, and a nationwide program including all non-vaccinated pregnant women in the country. These two latter scenarios were cost-effective if cost-savings due to avoided treatment costs for prevented complications were life-long, as shown in the sensitivity analysis. In the base-case analysis we included five years of cost-savings for prevented complications, a conservative assumption. However, 45% of costs due to congenital complications are expected to occur in the first five years of life (RIVM kosten van ziekten).

The saved costs are based on public data on treatment costs of congenital defects and are not specified for congenital defects due to rubella infection, leading to a somewhat uncertain estimate of costs that could be saved. Other societal costs not included in this analysis are the cost of physical adjustments to the home or special arrangements at school, e.g. extra teachers or special education for a disabled child. Due to lack of reliable data, production losses due to long or short term absence from work by parents taking care of a disabled child are also not included. The inclusion of such prevented costs would lead to a more favourable cost-effectiveness ratio. No indirect cost savings, i.e. production losses, were included due to lack of reliable data.

A survey among young women in one municipality in the region where rejection of vaccination is often made because of religious reasons showed that about 17% (2/12) would be willing to receive a MMR vaccination (Ruijs et al. 2009). The sensitivity analysis showed that the difference between our assumption (i.e. 20%, based on the preliminary results from study (Ruijs et al. 2009)) and the later results did not influence the results substantially. However, the willingness to vaccinate would probably be even lower for women belonging to the orthodox protestant groups because the women who accepted the MMR vaccination did not belong to these groups (Ruijs et al. 2009). This study showed that the willingness to vaccinate would have to be at least four per cent among the non-vaccinated women belonging to the orthodox protestant risk groups in the LVR for Scenario 1 to be cost-effective. If lower, the cost-effectiveness ratio would increase above the unofficial cost-effectiveness limit of €20,000 seemingly employed in the Netherlands.

Assumptions on the occurrence of rubella epidemics greatly influence the cost-utility estimates. If no outbreak would occur during the 16-year period, Scenario 1 would no longer be cost-effective. As the epidemiology of rubella in the Netherlands has changed since the introduction of vaccination, it is difficult to make predictions about occurrence of future outbreaks. No extensive sensitivity analysis was performed on this aspect, since the disease burden is strongly correlated with the inter-epidemic interval: a longer interval would increase the incidence of complications since the sero-prevalence in pregnant women would be lower. Furthermore increasing the time period would also increase the uncertainty of the estimates of the cost-effectiveness.

Regrettably, only the data from the outbreak in 2004–2005 was detailed enough for such an analysis.

The health-related QoL weights should ideally be preference based, estimated by a validated QoL instrument. Due to a lack of such estimates for the specific CRS defects, disease burden estimates were used and converted into a QALY estimate. These disease weights are country specific for the Netherlands, and originate from the same source (based on a panel of experts) (Melse et al. 2000).

Ad hoc screening in pregnant immigrant women and women in the LVR already takes place, but the extent of this is not documented. This practice may have lessened the number of pregnant women getting infected during the epidemic of 2004–2005. Consequently, if the recommended policy would entail screening only pregnant women in the LVR, thus excluding immigrant women outside the LVR, there could possibly be more infants born with rubella defects during an epidemic. We therefore recommend that this unofficial practice and the consequences of its cessation are assessed before recommending ceasing any current screening practices.

Immigrant girls (up to 12 years of age) and young women (up to 18 years of age) are vaccinated against rubella when entering the Netherlands. On ethical grounds it can be argued that all immigrant women of childbearing age should be screened and vaccinated if necessary, as they are entitled to the same protection against preventable infectious disease as the native population.

If the screening and vaccination program against rubella is implemented, we believe a good alternative would be to offer screening at the regular antenatal visit where other screening also takes place. In fact, this assumption was made in our calculations, where we added no extra costs for blood sampling. One alternative for the post partum vaccination would be to vaccinate directly after the delivery or at the after-birth care of the mother. If that would be the case, the costs for vaccination would be lower since no extra GP-visit would have to be made, resulting in a more favourable cost-effectiveness ratio.

Another option would be to include screening and vaccination in a pre-conception advice as advised by the Health Council of the Netherlands (2007). One of the largest advantages would be that a foetus in the first pregnancy would also be protected.

Fundamental to our results is the assumption that there is a willingness to accept vaccination in order to protect future children. As all rubella cases in pregnancy during the 2004–2005 epidemic, were among unvaccinated, orthodox protestant women, the acceptance of vaccination in this group is extremely important. The acceptance among women – particular among the orthodox protestant risk groups – would have to be further investigated before implementation.

APPENDIX Chapter 6

Unit costs screening and vaccination program

Unit costs for the screening program are costs for the test and an honorarium. The blood sample would not entail extra costs since it would be part of the standard sample taken at the antenatal health care visits at about 12 weeks' gestation. It is further assumed that the vaccination is given by a general practitioner and that the sensitivity and specificity of the serological test is 100% (Table A6.1).

Estimation of average QALYs lost

The average number of QALYs lost was estimated for an unspecified complication using disability weights estimated for the Dutch population (Melse et al. 2000). Since one child can suffer from several defects due to the maternal rubella infection, the QoL weights are multiplied to arrive at an estimate for the combination of defects, the standard way of combining one or more defects into one weight (Baal et al. 2006). Number of QALYs lost is summed for the defects present in the epidemic of 2004–2005. The weighted average of these is then used as the measure of the potentially QALYs gained for one unspecified complication. (Table A6.2) The life expectancy at birth (78.8 years (46.2 years when discounted 1.5%)) was used to calculate the QALYs.

Estimation of average costs due to congenital defect

Unit costs per defect are based on total health care costs in 2003 for diagnoses of hearing disability, congenital heart defect and congenital central nervous system defect (CNS) for children aged 0-4 years, as found in the database, over cost of illness in the Netherlands, using the definition of costs 'Zorgrekeningen CBS'* (RIVM kosten van ziekten). To arrive at a cost per patient (unit cost per defect) we divide total costs per defect by number of hospital admitted patient aged 0-4 years with the diagnosis, respectively, from national statistics (CBS). Costs for the first five years from birth are included under the assumption that most of the health care costs are made in this period (45% of the costs of defects on the CNS and the heart appear in the first five years). Ninety five percent of these costs are for hospital costs, except for hearing defects, where 65% are hospital costs. The unit costs for hearing defects are slightly overestimated because there are more children with hearing defects than what is assumed based on number of hospital admissions. Possible medical costs for

* This is a broad definition of health care costs, including public welfare services (e.g. child care). Another system is the Health Care Account which does not include public welfare costs. For the age groups 0-4 years with diagnoses related to congenital defects the difference between these two accounting systems was small (less than 3%) and for our calculations it is negligible.

treatment due to spontaneous abortion are not included in the costs due to CRS defects. The average yearly costs are estimated at €32,600, which during five years is €156,900 (€163,000 un-discounted) (Table A6.3).

QALYs gained and costs saved in a non-epidemic year

Number of preventable complications in a non-epidemic year is based on the assumption that one pregnant woman is infected with rubella annually. The probability that infection leads to a complication is 1/3, and the probability that the infected woman belongs to the specific subgroup is 25% for native women and 75% for immigrant women (Hof et al. 2004). These aspects lead to the different probability of complications in each subgroup (Table A6.4, column E).

The preventable complications are dependent on the chance that it is the second pregnancy and the chance that the women in each group accept screening and vaccination, and the vaccine effectiveness (95% in all groups). Of the 32 infected women parity is known for 25 of them: 11 or more were expecting their second or more child (44%). These probabilities are multiplied by the average QALY estimates and costs respectively, and summed for each scenario. This results in potentially gained QALYs and saved costs per scenario (Table A6.4).

Tabel A6.1 Unit costs for screening and vaccination (€ price[a] level 2007)

Unit costs	€ 2007	Reference
Test IgG rubella	10.13	Diagnostic kompas
Honorarium test	5.69	Diagnostic kompas
Total cost per screening	15.83	
MMR-vaccin, incl 6% WAT and 'receptregelvergoeding'[b]	25.57	Diagnostic kompas
General practitioner visit	21.37	Oostenbrink et al. 2004
Total cost per vaccination	45.94	

a. Inflated with consumer price index
b. Reimbursement to pharmacy per recipe, € 6.10 (Stichting farmaceutische kengetallen)

Tabel A6.2 Number of lost QALY per defect and average per complication, based on rubella epidemic 2004-2005

					QALYs lost due to epidemic 2004-2005	
	Disability weight	QoL weight	Number with defect	Per defect undiscounted	Epidemic discounted	Epidemic undiscounted
Central nervous system (CNS)	0.50	0.50	0	39.4	-	-
Heart defect	0.13	0.87	0	10.2	-	-
Hearing disability	0.07	0.93	3	5.5	9.7	16.5
Heart defect + hearing disability	-	0.809	1	15.0	8.8	15.0
CNS + hearing disability	-	0.465	2	42.1	49.4	84. 3
CNS + heart defect + hearing disability	-	0.405	5	46.9	137.6	234.5
Spontaneous abortion	-	-	2	78.8	92.4	157.5
Total number of infants with complications	-	-	13	-	-	-
Total number of QALY	-	-	-	-	297.9	507.8
Average number of lost QALY per infant with complications	-	-	-	-	22.9	39.1

Tabel A6.3 Annual unit cost per defect and average cost of complications (€ 2007)

						Costs over 5 years	
	Total health care costs Millions[a]	Number children aged 0-4 with defect	Unit cost per defect	Number of defect in epidemic	Annual health care costs	Discounted	Un-discounted
CNS defect	4.8	228	20874	0	-	-	-
Heart defect	26.3	999	26369	0	-	-	-
Hearing disability	62.5	12665	4936	3	14807	71272	74036
Heart defect + hearing disability	-	-	31305	1	31305	150681	156524
CNS + hearing disability	-	-	25810	2	51620	248465	258099
Heart defect+ CNS + hearing disability	-	-	52179	5	260895	1255783	1304473
Total	-	-	-	11	358626	1726201	1793132
Average cost per infant born with complications					32602	156927	163012

a. Inflated from 2003 with consumer price index

Tabel A6.4 Number of QALY gained and saved costs in a non-epidemic year (€ 2007)

Scenario Sub-groups	Number of pregnant women	Number sero-negative women	Percentage susceptible women in native or in first generation non-west immigrant women	Probability complication in group	Number of complications per sub-group	Number of preventable complications	QALYs gained	Costs saved
	Column A	Column B	Column C	Column D	Column E = C × D	Column F	Column G = F × average QALY[b]	Column H = F × average cost[c]
Non-vaccinated native; LVR	1595	175	175/(175+15+40+151[a])=45.93%	0.25*1/3 = 0.0833	0.0383	0.00304	0.0697	477
First generation non-west immigrants; LVR	842	52	52/1581 =3.29%	0.75*1/3 = 0.2500	0.0082	0.00294	0.0674	461
Total: Non-vaccinated LVR	2437	-	-	-	-	0.0060	0.14	938
Non-vaccinated native; LVR	1595	175	45.93%	0.0833	0.0383	0.00304	0.0697	477
Vaccinated; LVR	14679	15	15/(175+15+40+151[a])=3.94%	0.25*1/3 =0.0833	0.0033	0.00117	0.0269	184
First generation non-west immigrants; LVR	842	52	3.29%	0.2500	0.0082	0.00294	0.0674	461
Total: LVR	17116	-	-	-	-	0.0072	0.16	1122
Non-vaccinated native; rest of NL	1889	40	40/(175+15+40+151[a])=10.50%	0.0833	0.0087	0.0031	0.0697	491
Non-vaccinated native; LVR	1595	175	45.93%	0.0833	0.0383	0.0030	0.0717	477
First generation non-west immigrants; NL	25506	1581	1581/1581 =100%	0.2500	0.2500	0.0893	2.0478	14021
Total: Non vaccinated NL	28990	-	-	-	-	0.0955	2.19	14989

a. This is number of sero-negative native pregnant women living outside LVR (143399*2.10%*(1-0.95)=151)
b. Discounted 1.5% (Table A 6.2)
c. Costs over five years, discounted 4% (Table A6.3)

Table A6.5 Association between SGP voters and number of rubella cases in the municipalities. The categories represent percentage SGP voters in municipality (Figure 6.1a and b). Relative rates are estimated using Poisson regression with over dispersion.

Category	Relative rate	95% confidence interval		p-value
		lower	upper	
0.2 - 0.5 %	21.9	1.5	319.4	0.024
0.5 - 1 %	62.7	4.6	858.0	0.002
1 - 2 %	99.5	7.3	1364.5	0.001
2 - 5 %	444.5	34.4	5748.9	0.000
5 - 10 %	652.6	49.7	8573.6	0.000
10 - 20 %	2328.5	181.8	29820.8	0.000
> 20 %	3473.8	241.6	49941.1	0.000

Chapter 7

Economic analysis of pertussis illness in the Dutch population: Implications for current and future vaccination strategies

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Vaccine 2009; 27: 1932-1937

INTRODUCTION

As in many industrialized countries (Celentano et al. 2005, Ntezayabo et al. 2003, Quinn & McIntyre 2007) pertussis is endemic in the Netherlands, despite high vaccination coverage in infancy (approximately 96%) for over fifty years. Vaccination in childhood protects against severe disease, however, due to waning vaccine induced immunity and possible pathogen adaptation (Mooi et al. 2001) Bordetella pertussis continues to circulate and an increasing incidence of pertussis in adolescents and adults has been observed in recent years Quinn & McIntyre 2007, Guris et al. 1999, Greeff et al. 2008, Skowronski et al. 2002, Yih et al. 2000). In many countries pertussis is a mandatory notifiable disease. However, as pertussis in adolescents and adults is often clinically not recognized, the true number of adolescent and adult patients is likely to exceed the notified number (Melker et al. 2006). Adults appear to be an important source of severe infection of pertussis in infants (Bisgard et al. 2004, Elliot et al. 2004, Wendelboe et al. 2007). To prevent pertussis infection in infants, and to reduce the disease burden in adolescents and adults, many countries are exploring the effectiveness of extending current childhood vaccination programs to target also adolescents and (specific groups of) adults (Forsyth et al. 2005).

For governmental policymakers not only health benefits, but also economic aspects are considered when setting priorities for the introduction of new vaccinations in a National Immunization Program (NIP). Economic evaluations of pertussis vaccination are often strongly affected by assumptions on the amount of unreported patients and lack of reliable input data (Purdy et al. 2004, Scuffham & McIntyre 2004, Caro et al. 2005, Lee et al. 2007, Lee et al. 2005a, Iskedjian et al. 2004). Although studies focusing on costs associated with hospitalizations (O'Brien & Caro 2005), nosocomial outbreaks (Calguar et al. 2006, Ward et al. 2005) and specific subgroups (Lee et al. 2004, Lee et al. 2000) are available, no study includes all direct costs caused by pertussis infections in the general population.

This study aims to describe age-specific health care utilization and costs associated with pertussis in the Netherlands, taking into account costs for patients who are not registered in the routine notification system. Furthermore, we retrospectively evaluated the cost-utility of the preschool booster vaccination introduced in the Netherlands in the end of 2001 (Greeff et al. 2008). These data are essential for the decision making process regarding prospective vaccination strategies against pertussis.

METHODS

Study population and disease burden

The number of patients with pertussis in the Netherlands in the period 1998-2005 was estimated from two patient registries: the mandatory notification system and the continuous morbidity registration (CMR). The case definition for mandatory

notification includes a clinical picture compatible with pertussis (i.e. serious cough with a duration of more than two weeks and/or coughing attacks and/or cough followed by vomiting) in combination with: isolation of *B. pertussis* or *B. parapertussis*; detection of *B. pertussis* or *B. parapertussis* DNA by PCR; a significant rise in IgG antibodies against pertussis toxin (PT) or IgA antibodies against whole cell sonicate of *B. pertussis* in paired serum samples; a single serum sample with IgA/IgG-PT titres above a defined age-specific cut-off value (Melker et al. 2000); contact in the last three weeks with a patient with laboratory confirmed *B. pertussis* or *B. parapertussis* infection.

To adjust for underreporting, mandatory notifications were complemented with the number of patients registered in the CMR coordinated by the Netherlands Institute of Primary Health Care (NIVEL). The CMR is a registration of general practitioners (GPs) covering approximately 1% of the Dutch population, a representative sample of the population in terms of age, sex, and degree of urbanization. The GPs in this sentinel network weekly register the number of patients diagnosed with pertussis, divided into laboratory-confirmed (by paired or single sample serology, culture and/or PCR) and clinical cases. Age-specific incidence rates from the CMR were extrapolated for the whole Dutch population (circa 16 million) using the number of inhabitants on 1st January for the corresponding years. In our calculations, we considered the difference between the number of cases in the CMR and the number of notified patients as the number of clinically or underreported cases. The number of deaths in the period of study due to pertussis (ICD-10 code A370, A371, A378 and A379) was obtained from Central Statistics in the Netherlands (CBS).

Health care utilization

Number of patients hospitalized and the median length (days) of hospital stay was obtained from the National Medical Register, by extracting all patients with main discharge diagnosis pertussis (ICD-9 codes 0330, 0331, 0338 or 0339). We assumed all hospitalized patients were notified.

Based on interim results of a household-contact study on sources of pertussis in infants ≤ 6 months of age (Greeff et al. 2007), the proportion of infants requiring treatment at an intensive care unit (ICU) was estimated to be 13% with median length of stay of 8 days. We assumed that no patients older than 6 months were admitted to the ICU.

The number of GP and specialist consultations per pertussis case and the proportion of patients receiving antibiotics or cough medicine was estimated from a previous study on the disease burden of pertussis among 353 children aged 0-9 years, 54 adolescents 10-18 years and 100 adults who were notified for pertussis in the Netherlands in October 1997- January 1998 (Neppelenbroek et al. 1999). This study showed that for notified children aged 0-9 years the percentages of 1, 2, 3, 4 or 5 GP consultations were 3%, 39%, 38%, 19%, 2% respectively. For adolescents and adults these percentages were 2%, 42%, 41%, 13%, 1%, respectively. Furthermore, it was shown that 33% of all notified patients aged 0-9 years and 20% of notified

cases aged ≥ 10 years had a single specialist consult in addition to consulting a GP. In 2001-2005, the method of laboratory confirmation was indicated on the notification form. For the preceding years the use of different diagnostics methods was assumed to be similar to the distribution of methods in 2001-2002. Finally, the proportion of notified patients receiving antibiotics in the 0-year olds, 1-9, 10-19, 20-44 and ≥45 year olds was 73%, 69%, 45%, 61% and 56% respectively. In the same age-groups the proportion receiving cough medicine was 40%, 46%, 41%, 46% and 44%, respectively.

Table 7.1 Direct medical costs per unit for pertussis, the Netherlands, € 2007

Health care resource		Costs
GP consult		21.37[a]
Specialist consult		63.89[a,b]
Hospital admission per day		371.15[a,b]
ICU admission per day		1781.18[a]
Laboratory tests		
	Serology	40 per test[c]
	PCR/Culture	99 per test[c]
Antibiotics[d,e]		
	0 yrs	13.73
	1-9 yrs	13.87
	10-19 yrs	16.45
	≥ 20 yrs	16.45
Cough medicine[d,f]		
	0 yrs	4.86
	1-9 yrs	8.78
	10-19 yrs	9.04
	≥ 20 yrs	9.04
Vaccine[g,h]		18.30
	Administration costs	6.20

a. Oostenbrink et al. 2004, adjusted to 2007 using CPI
b. Weighted average between regional and university hospital
c. Laboratory for Infectious Diseases and Screening (LCI), RIVM
d. Average costs per age group of the medicines recommended in the 2007 guidelines of the Dutch College of General Practitioners (NHG, http://nhg.artsennet.nl/), the Dutch Pharmaceutical review book 2006 (Farmaceutisch Kompas, http://www.fk.cvz.nl/) and disease specific fact-sheets of the Dutch Centre for Infectious Disease Control (http://www.rivm.nl/cib/infectieziekten/Pertussis/Pertussis_kinkhoest.jsp). Doses in children 0-9 years were calculated using the mean bodyweight obtained from age-specific growth curves (TNO/LUMC).
e. Azithromycin, erythromycin or clarithromycin
f. Noscapin, codeine or promethazin
g. A single acellular vaccine (http://www.fk.cvz.nl/)
h. The vaccine was given concomitantly, though as a separate shot, with a combined diphtheria, tetanus, inactivated polio vaccine (DT-IPV) booster

For hospitalized cases we counted one GP consult as it is common practice in the Netherlands to first consult a GP who – if necessary – refers the patient to the hospital. For clinically or underreported patients we counted – as a conservative estimate – only one GP consultation.

Costs of health care

The economic burden estimates in this study include only direct medical costs, i.e. costs originating from health care resource utilization. To estimate the cost-utility ratio for the preschool booster the vaccine and administration costs were also included. All costs per unit are presented in euros 2007 (Table 7.1).

Data analysis

In view of possible future vaccination strategies, total costs and costs per case are presented for different age-groups (<1, 1-9, 10-19, 20-44 and ≥45 years). To address the impact of the acellular pertussis preschool booster vaccination introduced in 2001, we compared the total costs by periods; i.e. 1998-2001 when no preschool booster was given vs. years 2002-2005 when the booster was included in the NIP. By clustering of these years, the effect of year to year fluctuations in the occurrence of pertussis was also minimised.

To relate costs for vaccinating all children at preschool age to cost savings due to less pertussis cases (or less severe illness, needing less health care), costs per case averted were calculated for the targeted age-group as: cost of vaccination plus medical costs in the period with booster minus medical costs in the period without booster, divided by the difference in number of pertussis cases between the periods. We assumed a vaccination coverage of 93% (Abbink et al. 2006).

Health gains due to the preschool booster vaccination were combined with costs in a cost-utility analysis and expressed as quality-adjusted life years (QALYs) gained. The health state values (variously called: utilities, preferences, strength of preference, index, weights, or quality of life weights), reflect the relative desirability of the health state and are measured on an interval scale, where 1 refers to full health and 0 refers to death. Health state values for pertussis were derived from a study by Lee and colleagues applying the time trade-off (TTO) technique (Lee et al. 2005b). As a conservative estimate we used the median values of disease health states corresponding to a 'mild' health state. Values for 'infant pertussis' (0.72) were used for 0-year olds, values for 'adolescents' (0.87) for age-groups 1-9 and 10-19 years and values for 'adults' (0.96) for patients aged 20 years and older. For all ages the duration of the health state was 8 weeks, corresponding to 8/52 years. Death was calculated as a loss of 4 lifeyears (length of registration period), but we also performed the calculations for the loss of a whole life, using life expectance at birth in 2005 of 78.8 years and a discount rate of 1.5% (resulting in 46.2 years) (CVZ).

Assuming that the health state with pertussis is P, the total number of QALYs lost over the period before the booster can be calculated as (and correspondingly for period after the booster):

$$\sum_{1998}^{2001} \text{QALYs lost} = (1 - \text{value}_{\text{State } P}) \times \text{duration of state } P \times \text{number of cases in state } P$$

The cost-utility ratio describing the cost per QALY gained due to vaccination can then be estimated:

$$\frac{\text{Cost}}{\text{QALY gained}} = \frac{\text{Vaccination cost} + \sum_{2002}^{2005}(\text{Health case costs}) - \sum_{1998}^{2001}(\text{Health care costs})}{\sum_{1998}^{2001}\text{QALYs lost} - \sum_{2002}^{2005}\text{QALYs lost}}$$

In the Netherlands, such a ratio is generally considered cost-effective for preventable diseases if below a threshold value of €20,000. Analyses were performed using SAS version 9.1 and Microsoft Excel.

RESULTS

Disease burden

Table 7.2 shows number of patients registered in the notification system and CMR, by age group and period. In 1998–2001 the number of patients with pertussis registered in the CMR was a factor 3.0 higher than in the notification system, in 2002–2005 the number was 1.5 higher. In all age groups the numbers of patients registered in the CMR decreased from 1998–2001 to 2002–2005, with a decrease ranging from 15% (≥45 years) to 65% (0 years). In the notification system the number of patients decreased among 0 year olds (13%) and 10 year-olds (26%), while a 40% increase was seen in adults aged 20-45 and a 68% increase in both 10-19 year olds and ≥45 year olds.

Five deaths due to pertussis were reported: one in 1998, three in 1999 and one in 2004, all were children less than three months of age.

Health care utilization

In table 7.3 the health care consumption for pertussis, per age-group and period is given. In the 8 years under study, GPs were on estimate consulted 173 thousand times with complaints diagnosed as pertussis, corresponding to almost 22 thousand GP consultations per year (Table 7.3). Children aged 1-9 years old accounted for 54% of all consultations, though this percentage decreased from 59% in 1998-2001 to 46% in 2002-2005. In 1998-2001 and 2002-2005 a total of respectively 20,955

Table 7.2 Number of reported patients with pertussis registered in the CMR and notification system in the Netherlands, by age-group and period (1998-2001 versus 2002-2005)

	CMR		Notified patients	
	1998-2001 number (%)	2002-2005 number (%)	1998-2001 number (%)	2002-2005 number (%)
0 year	3334 (5)	1165 (3)	995 (5)	867 (4)
1-9 years	36768 (57)	16511 (48)	12731 (59)	9484 (46)
10-19 years	9707 (15)	6602 (19)	3202 (15)	5367 (21)
20-44 years	8502 (13)	4923 (14)	2772 (13)	3874 (16)
≥45 years	5852 (9)	4963 (15)	1982 (9)	3333 (13)
Total	64163	34164	21682	22925

(97%) and 22,233 (97%) notified cases were laboratory confirmed. This suggests that one out of five GP consultations for pertussis led to laboratory confirmation in 1998–2001, and one out of three in 2002–2005.

The number of patients needing hospitalization also decreased between the two periods. In both periods, infants below one year of age accounted for 74% of all hospitalizations. Among 0-year-olds, 1-9 year-olds and 20-44 year-olds, the number of hospitalizations decreased when comparing the two periods, whereas in the other age-groups a slight increase was seen. The median length of hospitalization decreased with one day.

Cost of treatment

In the eight years of study, the direct costs for pertussis were ca. €14 million, corresponding to €1.77 million per year (Table 7.4). Total costs decreased from €8.4 million in 1998–2001 to €5.8 million in 2002–2005. The majority of costs were attributed to hospitalization including ICU admission. Costs for GP consultations accounted for 26% of all costs in both periods. In general, the absolute and relative contribution of costs for diagnostics, antibiotics and cough medicine were higher in 2002–2005 compared to 1998–2001.

Table 7.3 Utilization of health care by patients with pertussis in The Netherlands, by age-group and period (1998-2001 versus 2002-2005)

	1998-2001						2002-2005						
	Age groups						Age groups						Total
	0	1-9	10-19	20-44	≥45	Total	0	1-9	10-19	20-44	≥45	Total	1998-2005
GP consultations	3965	59275	14986	13080	9116	100422	1701	33364	15471	11451	10338	72325	172747
Laboratory tests													
culture/PCR	296	579	76	63	16	1031	296	540	199	110	85	1230	2261
paired serum	148	1601	308	220	216	2493	66	809	365	189	181	1610	4103
single serum	514	10099	2718	2377	1723	17431	464	7787	4671	3467	3004	19393	36824
Unknown/ epidemiological linked	37	452	100	112	27	728	41	348	132	108	63	692	1420
Antibiotics	730	8790	1451	1691	1110	13771	636	6548	2432	2363	1866	13845	27616
Cough medicine	398	5833	1301	1261	874	9668	347	4346	2180	1763	1470	10105	19773
Specialist consultations	74	4104	636	552	393	5758	88	3073	1069	781	653	5663	11421
ICU admission	116	-	-	-	-	116	70	-	-	-	-	70	186
Hospitalisation	997	296	22	14	16	1345	656	173	24	9	28	890	2235
median duration (days)	6	3	3	3	3	-	5	2	2	2	2	-	-

Table 7.4 Costs of health care for pertussis, by age-group and period (1998-2001 versus 2002-2005), € 2007

	1998-2001						2002-2005					
	Age groups					Total	Age groups					Total
	0	1-9	10-19	20-44	≥45	1998-2001	0	1-9	10-19	20-44	≥45	2002-2005
GP consultations	84724	1266457	320181	279469	194760	2145591	36353	712842	330556	214650	220869	1545270
Specialist consultations	4722	262157	40631	35239	25120	367869	5267	184358	64116	46884	39156	339781
Hopitalizations	2469625	396387	31548	21527	20784	2939870	1328713	168502	23382	8536	26723	1555856
ICU admission	1650509	-	-	-	-	1650509	991046	-	-	-	-	991046
Diagnostics	60722	589354	140921	119004	87790	998791	53128	429643	235769	164609	143072	1026221
Antibiotics	10018	121911	23867	27816	18258	201870	8730	90818	40005	38874	30704	209130
Cough medicine	1934	51217	11759	11402	7902	84214	1685	38154	19710	15935	13287	88772
Total costs	4283255	2687482	568908	494456	354614	8388715	2424921	1624316	713539	519488	473811	5756075

Pertussis in infants was responsible for 51% of total costs in 1998–2001 and 42% of total costs in 2002–2005. The 1-9 year-olds, 10-19 year olds, 20-44 year olds and ≥45 year- olds accounted in 1998-2001 for respectively 31%, 7%, 6% and 4% of the total costs, and in 2002-2005 these percentages were 28%, 12%, 9% and 8%, respectively. Over the period of study, the estimated mean direct medical costs per clinical case for 0-year olds, 1-9 year-olds, 10-19 year olds, 20-44 year olds and ≥45 year-olds were €1,491, €81, €79, €76, and €77, respectively. For the same age-groups the mean direct costs per notified case were €3,572, €162, €130, €131, €134, respectively.

Economic evaluation of preschool booster

The costs for vaccinating children with a preschool booster amounted to €18.7 million in 2002–2005. Among children aged 1-9 years the costs per case averted due to the preschool booster were estimated at €922. Taking into account that the preschool booster may also have reduced pertussis in infants <1 year, the costs per case averted were €830. Equation (2) resulted in a cost-utility ratio for the preschool booster vaccination of €43,463 per QALY gained in children aged 1-9 in the period of study. Including life years gained in infants < 1 year of age would yield a cost-utility ratio of €30,855 per QALY gained, decreasing to €24,724 per QALY gained if calculating loss of expected life years at birth (discounted with 1.5%).

DISCUSSION

To the best of our knowledge this is the first study that attempts to estimate the national burden of pertussis in monetary terms. Our results show that annual costs for pertussis are still considerable (approximately €1.77 million) and do not substantially deviate from those of varicella zoster virus (€1.2 million for varicella and €3.0 for zoster) (Melker et al. 2005) for which inclusion in NIP is currently under consideration. As shown before (O'Brien & Caro 2005, Pichichero & Treanor 1997, Edmunds et al. 2002), the majority of costs for pertussis are incurred by costs for hospitalization and infants account for the bulk of these. Thus, despite the high disease burden in both children and adults, the economic burden of pertussis is largely determined by costs per infant case (€1,490) and only to a limited degree by costs per patient in other age-groups (circa €75).

Costs per case calculated in our study are lower than reported in previous studies from the US (Lee et al. 2004, Lee & Pichichero 2000). Although charges for medical consumption differ across countries and exchange rates may fluctuate, hampering direct comparison of costs, the costs per case also depend on the estimated level of underreporting of clinical patients (Caro et al. 2005). Acknowledging the fact that the true contribution of underreported or under-diagnosed patients may even be more substantial Melker et al. 2006), we think that with inclusion of the CMR estimates our results give a more complete picture of the medical costs of pertussis in

the society. First of all, CMR estimates are less likely to be hampered by under recognition since participating GPs are asked to weekly report pertussis and therefore will be more alert for the disease. Secondly, CMR estimates were validated by estimates from other sources: based on an additional questionnaire we know that in 2001-2005 the total number of laboratory confirmed patients in the CMR (45-65%) almost equaled the total number of notified patients in these years (data not shown), justifying our assumption that all laboratory confirmed cases in the CMR were notified. Likewise, estimates of the number of laboratory confirmed cases in the CMR corresponded with the number of positive patients according to the diagnostic serology database for pertussis at the RIVM (data not shown).

Remarkably, the number of patients registered in the CMR shows a decreasing trend in recent years, while the number of notified patients has increased, especially among adolescents and adults. We have no full explanation for the conflicting trends in the number of patients reported according to the CMR and notification system. The narrowing gap between the number of patients in the CMR and notifications, suggests improved alertness and/or reporting practice, implying that our estimates of the costs for the period before 2001 underestimate the actual costs for pertussis in that period. On the other hand, the slightly increased number of hospitalizations in adolescents and adults might suggest that part of the increase of notified patients may indicate a real increase of more typical – and probably better recognizable – pertussis disease in this group ((Ntezayabo et al. 2003, Skowronski et al. 2002, Yih et al. 2000).

Following the trends in disease burden, the costs for GP consultations and diagnostic testing in adolescents and adults have started to contribute more to the total economic burden of pertussis in recent years. In contrast, the absolute and relative contribution of costs for hospitalization has decreased in the Netherlands. This is partly related to a general tendency to shorten hospitalizations and discharge patients on an earlier stage (CBS). The absolute decline in hospitalizations among infants in recent years, is most likely due to a herd immunity effect of the preschool booster vaccination (Greeff et al. 2008).

In addition to estimating the economic burden of pertussis we have evaluated the cost effectiveness of the pre-school booster introduced in 2001. Our results show that this acellular preschool booster vaccination was not cost-saving within the framework of the NIP. Recognizing that an intervention does not have to be cost-saving to be worthwhile implementing, we also performed a cost-utility analysis. This showed that the preschool booster was a little over the limit of being cost-effective when taking into account also the observed herd-immunity effect in young infants. However, the quality of life values used might include altruism when parents are asked to value states for children (Lee et al. 2005b), and this may underestimate the value of the health state and overestimate the QALYs gained. Despite this and other reported shortcomings by Lee et al. (2005b), these values were used in lack of more reliable data. Conversely, it may also be argued that we underestimated the health gain by the preschool booster, when only including the health gain in the four years of study. Edmunds and colleagues (2002) showed by using a dynamic transmission model that a booster vaccination for 4 year olds could potentially be cost-effective

depending particularly on the number of deaths prevented and on the size of the herd-immunity effect in infants and children. Obviously, surveillance has to be continued to monitor the eventual long term effects of the pre-school booster.

Since recent studies have shown that in the Netherlands pertussis was often diagnosed too late to start antibiotic prophylaxis of family members at high risk (Niessen et al. 2008) and the acellular vaccine was well tolerated (Bults et al. 2007) costs associated with prophylactic treatment and QALYs lost to negative side effects are likely to be negligible.

We acknowledge there are still uncertainties around our estimates of disease burden and assumptions on health care utilization. Furthermore, in our calculation of costs we did not include indirect costs (loss of work productivity), while these may add substantially to the overall costs (Purdy et al. 2004, Lee & Pichichero 2000, Pichichero & Treanor 1997, Edmunds et al. 2002). However, preliminary results from a household study conducted in the Netherlands (Greeff et al. 2007) show that only 11/175 laboratory confirmed adult pertussis cases stayed at home for one or more days because of infection (unpublished data). Still, our results show that costs of pertussis in adolescents and adults are relatively confined and prevention of pertussis in infants will be the most effective way to save expenses. More importantly from a public health point of view, these infants are the ones suffering from the most severe disease sometimes leading to death. Vaccinating adolescents and adults, as often suggested (Forsyth et al. 2005, Lee et al. 2005a, Van Rie & Hethcote 2004), may reduce circulation of *B. pertussis* and hence transmission to vulnerable infants. Due to waning vaccine induced immunity boosting has to be repeated. This would be an expensive strategy of which the (cost) effectiveness is mainly determined by the level of herd-immunity attained, the true incidence and the duration of immunity (Caro et al. 2005, Lee et al. 2005a, Lee et al. 2008). A recent review suggested that, considering the substantial costs necessary to implement population based vaccination strategies for pertussis, these are unlikely to be cost-effective (Rodriguez-Cobo et al. 2008). We believe it will be more advantageous to focus exclusively on directly preventing transmission to infants, i.e. by vaccinating adults who are in close contact with newborns. Although the (cost)effectiveness still has to be investigated one can hypothesize that costs for vaccinating certain target groups will be lower than for decennial boosting of all adults. Moreover, feasibility of this approach might be better as young parents can be motivated during pre-natal health care visits. For the long term, resources should be used to study the possibilities to protect young infants earlier in life, by vaccination shortly after birth (Knuf et al. 2008, Siegrist 2008) or through maternal antibodies induced by vaccination of the mother during pregnancy (Mooi & Greeff 2007). Ultimately, the development of improved pertussis vaccines which induce long term immunity is required to tackle the pertussis problem.

Chapter 8

General discussion

OBJECTIVE AND BRIEF RESULTS

Cost-effectiveness analyses of vaccination against infectious diseases in the Netherlands are warranted to support decision-making on whether or not to include particular vaccinations in the National Immunization Program (NIP) (Houweling et al. 2010). The aim of vaccination at the population level is to prevent disease in the whole country. Widespread participation in a national immunization program creates herd immunity, which is expected to extend protection to non- or sub-optimally vaccinated individuals. It is important to incorporate this indirect coverage in a cost-effectiveness analysis, and this is one of the issues we address here.

The objective of this thesis is to evaluate the cost-effectiveness of different preventive measures and interventions against selected infectious diseases from a public-health perspective. Specific diseases were chosen to shed light on public-health issues in the Netherlands, the most recent being contingency planning for a possible influenza pandemic. We developed a dynamic transmission model for influenza and then applied it to a range of possible interventions against pandemic influenza, including the use of antiviral drugs and vaccination. Our results, in conjunction with those found in the literature, show that prevention and pharmacological interventions (i.e., vaccination and treatment with antiviral drugs) are cost-effective when targeted at reducing transmission or ameliorating the complications of illness.

Another issue concerning the NIP is what to do when certain groups refuse vaccination or when a vaccine is not effective enough to achieve the desired protection. For instance, infectious diseases can break out in pockets of non-vaccinated individuals, as happened during the rubella (German measles) epidemic of 2004-2005 in a low vaccination region (LVR), where several babies were born with complications due to infection in the mother (congenital rubella syndrome). We examined whether implementing a screening and vaccination program against rubella in that region would be a cost-effective means to prevent complications in unborn children. Our results indicate that for certain groups it would indeed be cost-effective. However, we also found that its cost-effectiveness would be highly subject to the willingness among eligible women to accept vaccination.

Pertussis (whooping cough) has proven difficult to control. Waning vaccine-induced immunity poses a threat not only to the individuals who are no longer protected but also to their close contacts when the anticipated herd immunity effect declines along with waning immunity. Infants less than one month of age are highly vulnerable to the disease and very difficult to vaccinate effectively. A booster vaccination in four-year-olds has reduced the number of pertussis infections overall, including in infants. Nevertheless, our results suggest that this prevention strategy has not been cost-effective.

THE IMPORTANCE OF DYNAMIC MODELS

A dynamic model, as opposed to a static one, takes the transmission of a virus into account; that is, it captures the very essence of communicable diseases. This makes a critical difference in the cost-effectiveness ratio, as shown in Chapter 4. When we applied the static model, we adjusted the size of the epidemic (the clinical attack rate, i.e., the share of the population that is symptomatic) but that did not change the cost-effectiveness ratio. Conversely, the cost-effectiveness ratio of the dynamic model was very sensitive to changes in size.

Our review of the international literature on economic evaluations of interventions within various pandemic influenza scenarios revealed that only a few of the analyses are based on dynamic models. In most studies, intervention proves to be cost-effective, also in those that do not apply a dynamic model (Chapter 5). Most studies foresee great benefits, economic as well as for health, of pharmaceutical intervention. Potential economic benefits of other transmission-reducing measures – such as closing schools, restricting travel, or imposing similar social-distance measures – were less evident, but they have also been explored less in the literature. These kinds of interventions are often brought up as possible measures to effectively reduce transmission.

The proportion of the population that is vaccinated needs to be large enough to create herd immunity, whereby unvaccinated individuals are also protected. The threshold for herd immunity differs among the infectious diseases, depending on their transmissibility. That is, the more new infections that are caused by one infected person (expressed in the reproduction number, R_0), the higher the vaccination coverage must be to eradicate the disease.

Herd immunity is an external effect – in this case a positive externality (i.e., an external benefit) – of vaccinating at the population level. An external effect occurs when a third party – someone who is not involved in the intervention – is affected by it. In the case of vaccination at the population level, the participating individuals bear the cost of vaccination (e.g., the risk of side-effects), whereas unvaccinated persons enjoy the benefit, namely less exposure at no cost. The positive externality can lead to a 'free-riding' problem, meaning that someone intentionally rejects vaccination knowing that the risk of getting infected is lowered through the herd immunity effect. This person knows that he or she is protected but avoids the cost of protection. However, if vaccination rates fall under protective levels in the population, notably due to massive rejection of vaccination, the indirect protection falls away (Geoffard & Philipson 1997, André 2003).

Vaccination can also have negative effects, some of which can be visualized with dynamic models. A case in point is the current debate on vaccinating young children against the varicella-zoster virus. Eliminating infection early in life, when infection is usually mild, would erase the natural booster effect among persons who had already been exposed. If a person who is already exposed and is latently carrying the virus has declining immunity, the virus can reactivate and cause zoster, a more severe disease. This, in turn, leads to a higher disease burden and more deaths. When captured in a dynamic model, these effects are evident, whereas they would not show up in a static

model. Thus, a favorable cost-effectiveness of vaccination as calculated with a static model would be a misleading outcome (Brisson & Edmunds 2006). Vaccination leads to a shift in the age of infection. If it moves into age groups where production losses may occur due to absence from work, cost-effectiveness analyses may yield a different result, vaccination being less cost-effective. Pertussis infection is a good example (Edmunds et al. 2002). Another possibly negative effect of vaccination is serotype replacement, as seen with vaccination against pneumococcal disease (Beutels et al. 2008). If the disease burden remains unchanged due to this replacement – i.e., if other serotypes continue to cause disease – the cost-effectiveness may be less than expected (Melegaro et al. 2010).

A key concept in dynamic modeling is the force of infection, which denotes the per capita rate at which susceptible individuals contract the infection. When fewer people are infected, the force of infection decreases. Generally speaking, if prevention against an infectious disease were not expected to have any influence on the transmission and the force of infection, a static model would suffice (Welte et al. 2005, Edmunds et al. 1999). This would apply to interventions in small groups, for instance to screening and treatment programs against chalmydia infections in pregnant women (Welte et al. 2005). It has been suggested that a static model would be suitable when evaluating the cost-effectiveness of including children or adolescents in vaccination campaigns against hepatitis B in low-endemic countries, whereas an illness such as influenza needs to be evaluated with a dynamic model (Beutels 2001). A dynamic model has one drawback: it requires more information, e.g., about contacts between individuals, than a static model. Being more complex, dynamic modeling calls for special mathematical expertise, making a dynamic model more expensive to develop (Welte et al. 2005).

We have contributed to the discussion about whether to use a static or a dynamic model by giving due attention to the implications of changing some of the circumstances regarding clinical attack rate and drug uptake. This brings important information to bear on any policy decision regarding an optimal drug (or vaccine) purchase as well as on expectations about uptake in the population. Specifically, when planning for an adequate stock of antiviral drugs to deploy during a probable pandemic, assumptions about the proportion of patients who would take antiviral drugs are crucial when calculating the cost-effectiveness of stockpiling (Chapter 3).

In the pandemic influenza context, we have offered insight into the influence on cost-effectiveness of vaccinating groups of individuals who are deemed responsible for a large part of the transmission (Chapter 2). One of the indirect effects of expanding the coverage would be less illness among other groups, and this is important for estimating the cost-effectiveness of the intervention. From a policy perspective, this is vital information for allocating resources and determining a vaccination strategy.

TARGETING VACCINATION IN PANDEMIC CONTROL

We found that all cost-effectiveness ratios (incremental cost per QALY gained, comparing intervention to no intervention) for different pandemic scenarios were below the accepted country-specific thresholds when the effects were calculated for the total population (Chapter 2). We also found that in a pandemic scenario involving the possibility of an early vaccination with no immunity among the population vaccinating elderly would be the most cost-effective strategy in Germany, a country with relatively more individuals aged 65 years and older compared to the Netherlands and the United Kingdom. For the two latter countries it would be more cost-effective to vaccinate high transmitters in the same pandemic scenario. A general recommendation from an international organization may be useful comparing cost-effectiveness for culturally close countries, but should be considered with due caution. If demographics are different, pre-existing immunity can change the cost-effectiveness of intervention. With an aging population, this information needs to be considered in the contingency planning for future pandemics.

IMPROVING IMMUNITY IN INDIVIDUALS NOT PROTECTED BY HERD IMMUNITY

Unfortunately, even in a highly successful national immunization program such as that in the Netherlands, there are still individuals who remain unprotected against some diseases. If women of childbearing age who do not have protective antibody levels against rubella can be convinced of the advantages of vaccination, both the afflicted children and their parents could be spared much suffering. These women are mainly found in clusters of non-vaccinated individuals where regular outbreaks of infectious diseases occur, diseases that have almost disappeared in the rest of the population. We found that screening and vaccination of unprotected women in low vaccination regions, but not at the national level, would be cost-effective (Chapter 6). Yet the question remains how to convince people to be vaccinated.

An outbreak of pertussis among children, adolescents, and/or adults may strike the vulnerable, not yet vaccinated group of newborns. We retrospectively investigated the cost-effectiveness of the booster vaccination that was introduced in the Netherlands in 2002 among four-year-olds. It was not found to be convincingly cost-effective. At present, discussions about pertussis concern the vaccination of individuals in close contact with newborns, e.g., certain health-care workers and pregnant women. Another option being discussed is the revaccination of adolescents to reduce prevalence in the population. If more resources are to be spent to protect infants against serious illness due to a pertussis infection, the cost-effectiveness should first be evaluated.

OTHER ISSUES

A traditional cost-effectiveness ratio does not include allocation aspects in other publicly funded areas. Indeed, the cost per life year gained is difficult to compare to investments in, for instance, educational systems. Many of our conclusions about the cost-effectiveness of interventions (especially stockpiling) rely heavily on the strict employment of a threshold value: the acceptable cost per (quality-adjusted) life year gained. But the validity of tying cost-effectiveness to an arbitrary limit such as that value is a topic on which we do not elaborate here.

Another point that has not been raised in this thesis concerns the ethical aspects of cost-effectiveness estimations. Questions like "who is gaining how many life years or how much health-related quality of life due to an intervention?" are currently under discussion. For instance, is one (quality-adjusted) life year gained for an 85-year-old worth just as much as for a 45-year-old? Society might be willing to pay more – i.e., to accept a higher cost per (quality-adjusted) life year gained – to avoid infection in an infant than in an elderly person. In the case of the influenza pandemic, we saw that vaccinating only the elderly would lead to fewer deaths in that category than vaccinating the groups responsible for much of the transmission. In many situations, however, it would be more cost-effective to vaccinate the latter.

It is standard procedure to apply discount rates to future costs and benefits in economic evaluations in general (e.g., in cost-benefit analyses of capital investments), and health-economic evaluations are no exception. But there, not only the costs but also the life years gained are discounted (Bos et al. 2004, Bos et al. 2005). Discounting reflects the belief that your future earnings and costs are valued less than earnings you receive and costs you pay today. Consequently, applying a low discount rate for life years gained will make years further in the future count more than they would if a high discount rate were applied. Costs incurred today for vaccinations would then be spread over more life years gained at a lower discount rate, thereby lowering the cost-effectiveness ratio and making the preventive measure more attractive than if the life years gained had been discounted at a higher rate. The Netherlands applies a lower rate for discounting life years (1.5%) than for costs (4%) (Oostenbrink et al. 2003).

Besides cost-effectiveness, other considerations will always be part of a decision, as they should be. For instance, keeping a stock of antiviral drugs to control an influenza pandemic might be desirable on ethical grounds. However, keeping too large a stock of vaccines or antiviral drugs is a waste of resources that could be better spent on other publicly funded undertakings or on private consumption. It is not obvious that society would be willing to pay more than normally considered acceptable for other health-promoting treatments just to know that a potentially effective drug will be on hand during an influenza pandemic. If a value could be placed on the (sense of) security drawn from keeping a stock, it could be incorporated into a cost-effectiveness analysis. This is a topic to be addressed in future research.

CONCLUDING REMARKS

Herd immunity should be given due attention in economic evaluations of measures against the transmission of infectious diseases, principally because the public-health interventions aim at protecting the whole population. Dynamic epidemiological models provide a basis for estimating the impact of this effect. It may be expected that dynamic models will be used more from now on in conjunction with economic evaluations, whereby collaboration between health economists and mathematical modelers is crucial.

There have been claims that dynamic modeling may not be necessary to estimate the cost-effectiveness of preventive measures that produce positive external effects. The use of a static model would be good enough since the effect of intervention are actually even greater (e.g., due to herd immunity). In line with that reasoning, it follows that the cost-effectiveness ratio would only be more favorable when external benefits are included. We would refute the validity of that argument, however. The standpoint that a lower cost-effectiveness ratio only makes an intervention more attractive and therefore deserves to be implemented leads to a sub-optimal solution, which ignores opportunity costs. It could prompt excessive allocation of resources for preventive measures, since an equal number of life years gained could be attained with less investment. The resources could then be used for other purposes such as public or private consumption. Therefore, to avoid a skewed allocation of public funds, positive and negative external effects of vaccination need to be included in economic evaluations, which will ultimately improve public resource allocation.

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Summary

The objective of this thesis is to explore the cost-effectiveness of controlling epidemics and preventing outbreaks of infectious diseases. Preventive measures and interventions against selected infectious diseases are investigated from a public health perspective. The selection reflects topics of current interest in the Netherlands. One of these is contingency planning for an influenza pandemic. Other urgent concerns regard protecting infants against congenital rubella syndrome, which is caused by rubella (German measles) infection in the mother during pregnancy, and preventing infants from infection with pertussis (whooping cough).

Recent technological progress has produced a range of vaccines that have greatly improved public health, mentioned in **Chapter 1**. The question is whether they – or perhaps all such measures for intervention or prevention – are worthwhile from a social and economic perspective. In other words; is the cost of preventing disease acceptable given the amount of health gained? In that light, cost-effectiveness analyses are warranted to support decision-making on whether or not the National Immunization Program (NIP) should include a new vaccination or change an existing vaccination scheme. If cost-effectiveness ratio comparing an intervention with normal treatment (or no treatment) lies below a certain threshold value, the intervention is considered cost-effective. In the Netherlands, a rule of thumb for preventive measures is that a life year (or quality-adjusted life year, QALY) is worth €20,000.

In **Chapter 2** the effects of vaccination against a pandemic influenza virus for three West-European countries is estimated. The aim is to investigate the cost-effectiveness of several vaccination strategies compared to no vaccination for different pandemic scenarios to ascertain which one would be most cost-effective. A dynamic deterministic age-structured SEIR (Susceptible, Exposed, Infected, and Recovered) transmission model is therefore linked to an economic model. The scenarios include the timing of the availability of the vaccine (before or during the pandemic) and a possible pre-existing immunity among the elderly. There are three strategies: vaccinating the whole population; only the elderly; only children aged 5-19 years (the 'high-transmitters'). The SEIR transmission model incorporates country-specific demographic characteristics and social contact patterns, and the health-care consumption and unit costs for health-care resources are specific to Germany, the Netherlands, and the United Kingdom. The most cost-effective strategy differs across the pandemic scenarios and to some extent among the countries. Under special circumstances – for instance, if the demographics are substantially different – a pre-existing immunity might alter the cost-effectiveness of intervention, as seen in Chapter 2.

The cost-effectiveness of stockpiling antiviral drugs to use during an influenza pandemic is investigated and presented in **Chapter 3**, again the effectiveness is estimated with a dynamic model. Stockpiling over 30 years is estimated, including the risk of a pandemic during that time frame. Stockpiling is cost-effective if the risk of a pandemic is greater than 9% during the 30-year period, taking avoided production losses into account. The presumed risk of a pandemic is very important in the decision whether or not to invest in a stock of antiviral drugs. Furthermore, the cost-effectiveness of stockpiling is influenced by the coverage of antiviral therapy in

the population, as it limits the spread of infection. In the event of lower coverage or a higher attack rate, stockpiling remains cost-effective.

Aspects of the cost-effectiveness of the therapeutic use of antiviral drugs to treat influenza-like illness during an influenza pandemic is presented in **Chapter 4**. The first step is to compare the dynamic age-structured transmission model to a static model. Then the sensitivity of epidemiological factors and aspects of drug coverage with respect to the cost-effectiveness ratios for each of the two models is examined. Therapeutic use of antiviral drugs is more cost-effective compared to non-intervention, irrespective of which model is applied. Some key findings are that the cost-effectiveness ratio according to the static model is insensitive to the size of a pandemic whereas the ratio according to the dynamic model increases with the size of a pandemic. That is, applying the dynamic model, the cost-effectiveness of the intervention depends on the proportion of the population that is infected and symptomatic (the clinical attack rate) and subsequently treated. This has implications for policy decisions such as on how large a stock of antiviral drugs should be in preparation for mitigating a pandemic.

In light of a review of the literature on the cost-effectiveness of controlling an influenza pandemic, an overview of the use of dynamic models and the results of cost-effectiveness studies is added in **Chapter 5**. Various interventions has been investigated: antiviral stockpiling and treatment and/or prophylaxis with these drugs, vaccination strategies; school closure; and restricting international travel. Their cost-effectiveness varies, but the economic profiles of these measures are generally favorable. For these calculations, more studies use static models than dynamic models. A recommendation that follows is that further research be directed towards linking dynamic epidemiological models for pandemic spread with economic outcomes in view of the impacts on national economies including the direct, indirect, medical, and non-medical costs.

Chapter 6 considers one obstacle in the otherwise successful NIP, namely the clusters of unvaccinated individuals in low vaccination coverage regions (LVRs). During an epidemic in the Netherlands in 2004–2005, 11 children were born with complications related to rubella infection in the mother during pregnancy. Many of these complications could have been prevented if the mothers had been vaccinated. Screening for rubella antibodies and offering vaccination to women without immunity could protect a subsequent fetus. Screening of unvaccinated women in LVRs could be cost-effective. Indeed, cost-effectiveness depends on the willingness to be vaccinated. Screening broader groups, e.g. including all unvaccinated women in the whole country, will not be cost-effective.

Chapter 7 presents the results of an economic evaluation of vaccination against pertussis. As in many industrialized countries, pertussis is endemic to the Netherlands despite high vaccination coverage in infancy. While vaccination in childhood protects against severe disease, it does not give life-long protection. This study has a dual aim: to estimate the cost of illness for pertussis; and to estimate the cost-effectiveness of the preschool booster vaccination strategy introduced in 2001. Although infants represent 5% of the cases, they account for nearly half the total cost. The retrospective cost-utility analysis of the booster strategy compares the period

1999–2001 with 2002–2006. The booster vaccination was not found to be cost-effective despite the substantial reduction in number of cases in the total population and in particular the reduction among infants. The cost-effectiveness of vaccination strategies to reduce the burden of disease on infants relies to a large extent on the herd immunity effect, since it is not always feasible to vaccinate newborns. Before implementing alternative strategies to protect infants, for instance by vaccinating close contacts or revaccinating adolescents, the cost-effectiveness of such strategies needs to be evaluated.

Repeatedly in this book, attention has been drawn to the importance of including herd immunity effects in economic evaluations of preventive measures against the transmission of infectious diseases. In **Chapter 8** this, among other things, is discussed. Herd immunity is a positive external effect of a population-wide vaccination program. An external effect occurs when a third party – that is, someone not involved in the intervention – is affected by it. There are also negative effects connected to vaccination at the population level. One example is a shift in the age of infection; another is serotype replacement due to vaccination. If such effects are included in the economic evaluation, the cost-effectiveness of vaccination may be less than expected.

External effects of vaccination can be estimated with dynamic epidemiological models. Therefore, we advocate dynamic modeling for economic evaluations of infectious diseases. We have contributed to the discussion about the importance of a dynamic model by showing the implications for cost-effectiveness of including clinical attack rate and drug uptake during an influenza pandemic. In the same context, we have also shown how cost-effectiveness is altered when choosing the strategy vaccinating groups who account for a large share of the transmission. From a policy perspective, this information is vital for allocating resources and deciding on a vaccination strategy.

There have been claims put forward that dynamic modeling may not be necessary to estimate the cost-effectiveness of preventing infectious diseases. The rationale is that the cost-effectiveness ratio will only become more favorable when including the external benefit of herd immunity, for instance. We dispute this reasoning. The argumentation that a lower cost-effectiveness ratio only makes an intervention more attractive and should therefore be implemented leads to a sub-optimal solution, neglecting opportunity costs. Actually, if an equal number of life years gained can be reached by using fewer resources, these freed resources could be applied to other objectives, whether for public or private consumption. External (positive and negative) effects of vaccination need to be included in the economic evaluation to improve public resource allocation.

Samenvatting

Dit proefschrift omvat een aantal studies gericht op de kosteneffectiviteit van het voorkomen en beperken van uitbraken van infectieziekten. Preventieve maatregelen en interventies tegen bepaalde infectieziekten zijn daarbij onderzocht vanuit een volksgezondheidsperspectief. Bij de selectie van de te onderzoeken controle-maatregelen en infectieziekten is vooral gekeken of deze een weerspiegeling vormen van actuele onderwerpen in Nederland. Eén van de onderwerpen die daarom is onderzocht is de voorbereiding ter beperking van de consequenties van een eventuele influenza pandemie. Andere problemen rondom infectieziekten die aandacht krijgen binnen dit proefschrift zijn de bescherming van foetussen tegen het congenitale rubella syndroom – hetgeen veroorzaakt wordt door rubellainfectie (rodehond) van de moeder tijdens de zwangerschap – en het voorkomen van pertussisinfectie (kinkhoest) bij zuigelingen. Beide problemen staan al langere tijd in de aandacht en vereisen mogelijk nadere maatregelen voor optimale controle van de problematiek.

In **hoofdstuk 1** wordt een historisch overzicht van vaccinaties en vaccinatie-programma's gepresenteerd die door nieuwe technologische ontwikkelingen tot stand zijn gekomen en de volksgezondheid hebben bevorderd. Een belangrijk vraagstuk daarbij is of alle nieuw ontwikkelde vaccins vanuit een maatschappelijk en economisch perspectief voldoende gezondheidswinst opleveren in relatie tot de hiermee benodigde kosten. Om die reden wordt tegenwoordig veelvuldig gebruik gemaakt van kosteneffectiviteitanalyses om tot een weloverwogen beslissing te komen om een nieuw vaccin wel of niet op te nemen in het Rijksvaccinatieprogramma. De uitkomstmaat die in zulke analyses centraal staat is de kosteneffectiviteitratio, waarbij een nieuwe interventie wordt vergeleken met de bestaande interventie. Als de ratio lager is dan een bepaalde drempelwaarde wordt de interventie als kosteneffectief beschouwd. Hoewel er geen officiële drempelwaarde bestaat in Nederland wordt voor preventieve maatregelen de vuistregel aangehouden dat de waarde van een gewonnen levensjaar (of voor kwaliteit van leven gecorrigeerd levensjaar, QALY)) minstens €20,000 is.

In **hoofdstuk 2** is het effect van vaccinatie tegen een pandemisch influenza virus onderzocht voor drie West-Europese landen, namelijk: Duitsland, Nederland en het Verenigd Koninkrijk. In het bijzonder is aan de hand van drie scenario's voor verschillende vaccinatiestrategieën onderzocht welke van de strategieën het meest kosteneffectief is in vergelijking met geen vaccinatie. De drie vaccinatiestrategieën zijn gericht op: de hele populatie, enkel de ouderen, enkel kinderen van 5-19 jaar oud (potentiële "superspreaders"). Hiervoor is een dynamisch deterministisch leeftijdsgestructureerde SEIR (Susceptible, Exposed, Infected, Recovered) transmissiemodel gekoppeld aan een economisch model. In de scenario's verschillen de mate van beschikbaarheid van een vaccin (vóór of tijdens de pandemie) en de mogelijke reeds aanwezige immuniteit onder ouderen. Het SEIR transmissiemodel bevat landspecifieke demografische eigenschappen en sociale contactpatronen. De gezondheidszorgconsumptie en kostprijzen voor de zorg zijn specifiek voor de drie landen. Welke vaccinatiestrategie het meest kosteneffectief is verschilt tussen de scenario's voor de verschillende landen. In hoofdstuk 2 laten wij zien dat de

kosteneffectiviteit anders uitvalt als er reeds immuniteit aanwezig is en als er bijvoorbeeld substantiële verschillen zijn in de demografie van de landen.

In **hoofdstuk 3** is de kosteneffectiviteit van het aanhouden van een voorraad antivirale middelen die gebruikt kan worden tijdens een influenzapandemie onderzocht. Ook in deze studie is de effectiviteit geschat met een dynamisch model. Voor de geschatte kans op een pandemie is uitgegaan van het aanhouden van een voorraad antivirale middelen voor een periode van 30 jaar. Het blijkt dat een voorraad aanhouden kosteneffectief is als het risico op een pandemie groter is dan 9% tijdens die 30-jarige periode en als daarbij kosten voor werkverzuim tijdens de ziekte worden meegerekend. Het geschatte risico op een pandemie is van groot belang bij de beslissing om wel of niet te investeren in een voorraad antivirale middelen. Daarbij wordt de kosteneffectiviteit beïnvloed door de dekking en het gebruik van de antivirale middelen in de populatie, omdat het gebruik de verspreiding van de infectie verminderd. Als de dekking lager zou zijn of als een groter aandeel van de bevolking ziek zouden worden, blijft een voorraad aanhouden nog steeds kosteneffectief.

In **hoofdstuk 4** wordt onderzoek gepresenteerd naar de kosteneffectiviteit van therapeutisch gebruik van antivirale middelen om influenza-achtige ziektebeelden te behandelen tijdens een influenza pandemie. Hier wordt nadruk gelegd op verschillen en overeenkomsten tussen berekeningen die uitgevoerd zijn met twee verschillende modeltypes. Dit is gedaan aan de hand van het schatten van kosteneffectiviteitratio's met behulp van een dynamisch model en een statisch model. Tevens is de gevoeligheid van epidemiologische factoren en aspecten van het gebruik van antivirale middelen op de ratio's van de twee modellen onderzocht. Het therapeutische gebruik blijkt kosteneffectief te zijn in vergelijking met geen interventie, ongeacht welk model wordt gebruikt. Belangrijke andere bevindingen zijn dat de kosteneffectiviteitratio in het statische model niet verandert als het aandeel van de bevolking dat geïnfecteerd is groter wordt, terwijl de ratio van het dynamische model toeneemt naarmate de pandemie in omvang toeneemt. Dit impliceert dat in het dynamische model de kosteneffectiviteit afhankelijk is van de proportie mensen in de bevolking die geïnfecteerd en symptomatisch is en vervolgens ook behandeld wordt. Dit heeft beleidsimplicaties met betrekking tot voorbereidingen gericht op het beteugelen van een pandemie, bijvoorbeeld wat betreft de omvang van het aanhouden van een voorraad antivirale middelen.

In **hoofdstuk 5** wordt een literatuurstudie met betrekking tot de kosteneffectiviteit voor het beheersen van een influenza pandemie gepresenteerd. Er wordt een overzicht gegeven van het toepassen van dynamische en statische modellen in de schatting van de kosteneffectiviteit van interventies tegen de verspreiding van een pandemisch influenzavirus. Onderzoek naar verschillende interventies is terug te vinden in de literatuur: het aanhouden van een voorraad antivirale middelen voor behandeling en/of preventief gebruik ervan, vaccinatiestrategieën, sluiting van scholen, en beperkingen van het internationale reisverkeer. De kosteneffectiviteit van deze maatregelen varieert, maar is in het algemeen gunstig. In de bestudeerde publicaties

van deze studies worden vaker statische dan dynamische modellen gebruikt. Een aanbeveling die uit deze literatuurstudie volgt is dat nader onderzoek verricht zou moeten worden naar de koppeling tussen dynamische modellen voor pandemieën met economische gegevens over de impact op nationale economieën, met het meenemen van directe, indirecte, medische en niet-medische kosten.

In **hoofdstuk 6** wordt een probleem – in het overigens verder zeer succesvolle Nederlandse Rijksvaccinatieprogramm – onderzocht, namelijk regionale clustering van niet-gevaccineerde individuen. Tijdens een epidemie in Nederland gedurende 2004-2005 werden 11 kinderen geboren met complicaties die gerelateerd konden worden aan een rubellainfectie van de moeder tijdens de zwangerschap. Veel van deze complicaties hadden voorkomen kunnen worden als de moeder gevaccineerd was geweest. Screening voor rubella antistoffen en het aanbieden van vaccinatie aan vrouwen die geen immuniteit hebben tegen rubella zou tijdens een volgende zwangerschap de foetus kunnen beschermen. De onderzoeksbevindingen laten zien dat screening van niet-gevaccineerde vrouwen in regio's met een lage vaccinatiegraad kosteneffectief zou kunnen zijn, hoewel de kosteneffectiviteit afhankelijk is van de mate waarin vrouwen bereid zijn zich te laten vaccineren. Het screenen van grotere groepen, bijvoorbeeld van alle niet-gevaccineerde vrouwen in het hele land, zou niet kosteneffectief zijn.

In **hoofdstuk 7** worden de resultaten gepresenteerd van een economische evaluatie van een interventie tegen pertussis. In Nederland, zoals in veel geïndustrialiseerde landen, is pertussis endemisch ondanks een hoge vaccinatiegraad in zuigelingen. Hoewel vaccinatie in de kinderjaren beschermt tegen ernstig ziekte, geeft het geen levenslange bescherming. Deze studie had twee doelstellingen: de zorgkosten van pertussis te schatten en het schatten van de kosteneffectiviteit van de vaccinatiestrategie bestaande uit een voorschoolse boosterinjectie. Ondanks het feit dat zuigelingen 5% van de gevallen uitmaken, zijn ze verantwoordelijk voor bijna de helft van de totale zorgkosten gerelateerd aan pertussis. De retrospectieve economische evaluatie van de boosterstrategie vergeleek de periode 1999–2001 met 2002–2006. De boostervaccinatie blijkt niet kosteneffectief te zijn volgens de gehanteerde drempelwaarde, ondanks de grote reductie van het aantal gevallen in de totale populatie en de reductie bij zuigelingen in het bijzonder. De kosteneffectiviteit van vaccinatiestrategieën om de ziekte bij zuigelingen te verminderen hangt grotendeels af van de groepsimmuniteit, omdat pasgeboren kindjes geen antistoffen hebben tegen pertussis. Voordat alternatieve strategieën ingevoerd worden om de zuigelingen te beschermen, bijvoorbeeld door het vaccineren van volwassenen in dicht contact met pasgeboren kindjes of het revaccineren van adolescenten, dient de kosteneffectiviteit van zulke maatregelen nader onderzocht te worden, bij voorkeur met dynamische modellering.

In **hoofdstuk 8** wordt het meenemen van externe effecten van vaccinatie in economische evaluaties van preventieve maatregelen tegen de overdracht van infectieziekten bediscussieerd. Een extern effect is een effect dat een derde persoon

treft; dat wil zeggen iemand die niet bij de interventie betrokken is. Groepsimmuniteit is een positief extern effect van een populatiebreed vaccinatieprogramma. Het houdt in dat ook niet-gevaccineerde individuen beschermd zijn tegen de ziekte omdat de ziekte minder circuleert in de bevolking en het risico een geïnfecteerde persoon te ontmoeten kleiner is. Er zijn ook negatieve externe effecten door vaccinatie op populatieniveau. Een voorbeeld hiervan is een verschuiving in leeftijd van infectie (zo is waterpokken ernstiger naarmate de leeftijd hoger). Een ander negatief extern effect is dat de ziekteverwekker waartegen gevaccineerd wordt vervangen wordt door een andere stam of andere soort ziekteverwekker die ook ziekte kan veroorzaken (bijvoorbeeld serotype vervanging bij pneumokokken). Als zulke effecten worden meegenomen in economische evaluaties zou de kosteneffectiviteit minder gunstig kunnen uitvallen.

Dynamische modellen, in tegenstelling tot statische modellen, zijn geschikt om externe effecten van vaccinatie te schatten. Ik heb met dit proefschrift een bijdrage willen leveren aan de discussie omtrent het belang van het gebruik van dynamische modellen door de implicaties hiervan op de uitkomsten van kosteneffectiviteit te laten zien. Daarom pleit ik voor het gebruik van dynamische modellen bij economische evaluaties van infectieziekten. Vanuit een beleidsperspectief is deze informatie cruciaal voor de verdeling van financiële en andere beperkte middelen en het nemen van beslissingen met betrekking tot vaccinatiestrategieën. Sommige onderzoekers redeneren dat dynamische modellen niet nodig zijn in deze context, omdat de kosteneffectiviteitratio's nog gunstiger zouden worden als positieve externe effecten zoals groepimmuniteit meegerekend worden. Ik zou deze redenering willen betwisten. Enerzijds omdat er negatieve externe effecten kunnen zijn die de positieve overheersen, maar anderzijds ook omdat het gebruik van statische modellen kan ertoe leiden dat een vaccinatiestrategie wordt gekozen die weliswaar kosteneffectief is, maar een dynamisch model zou kunnen laten zien dat een andere vaccinatiestrategie nog kosteneffectiever kan zijn. Externe (positieve en negatieve) effecten van vaccinatie moeten daarom worden meegenomen in economische evaluaties om tot een evenwichtige verdeling van publieke middelen te komen.

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Acknowledgement

This thesis is the result of a wish that began a long time ago. The ambition to write a thesis has been following me ever since my undergraduate studies at Lund University, Sweden. However, other plans and pursuits took precedence and the actual realization was time and again postponed. During my years at the Swedish Institute for Health Economics (IHE), where I began my career in health economics, the opportunity to combine my work with PhD-studies materialized. The studies resulted in the Licentiate of Philosophy degree in 2003. That same year, I moved to the Netherlands. Since 2005 I have been working at the department of Epidemiology and Surveillance at the Centre for Infectious Disease Control at the National Institute for Public Health and the Environment. Here my plans and wishes came to life again where, surrounded by a number of enthusiastic colleagues, this thesis came about.

I have benefited from the help of several people without whom this thesis would not have been possible. Maarten, in December 2008 I approached you to ask if you would like to be my 'promotor' (PhD supervisor). I am very pleased that you agreed! In you I found a rewarding cooperation, clearly seen by the publications included here. Even if the physical distance between Bilthoven and Groningen made our meetings somewhat infrequent, they were productive. Two years later, the thesis is a reality. I sincerely hope that we can continue working together after this collaboration has ended.

Jacco, my 'co-promotor' and boss, I want to thank you for making it possible. You have continuously encouraged me, and you never stopped believing in the whole enterprise. Among so many other things, your general knowledge impresses me. For instance, I did not know that the Bernoulli utility had such a close link to models predicting effects of vaccination, nor did I know the link to Groningen. What a funny coincidence.

I am of course also very grateful for the work that all the other co-authors have done, thank you all. In particular, Sido en Michiel, thank you for the dynamic models; Sabine, Liesbeth, Susan en Helma, thank you for the fruitful cooperation. Thanks Jan for sharing your statistical expertise. I also want to thank Jannie for helping with the administration in Groningen.

Members of the approval committee: Professors Roel Coutinho, Ulf Persson, and Jan Wilschut, thank you for your thoughtful comments and approval of the manuscript.

Fellow members of the modeling group at EPI; Anneli, Dennis, Hans, Hester, Maria, Marijn, Michiel, Rolf, Sandra, and Tjibbe; we have had a lot of laughs together at our meetings and coffee breaks. My roommates, Carolien, Françoise, Anja and Annelies you have heard all about rejected and accepted papers: thanks for giving the distraction needed every now and then. My EPI-colleagues, and our head of department, Marianne, you have been closely following the final stages of this work and asking me whether I had already set the date for my defense. Thanks Katie for the checking of my English. Thanks Henrik for checking the headings. All remaining linguistic errors are my own responsibilitie.

Furthermore, my old IHE colleagues, I often miss the funny times we had. Ulf and Anders, you made IHE a very nice place to work and you have inspired me to continue along the academic path. Catharina and Rosita, I am so glad that we are still in contact, even though we live in different parts of Europe, or even the world.

I also appreciate all the mental support from old and new friends. Danni, what would I do without your funny Friday emails? Iss and Anita, I have known you for as long as I can remember and we are still the very best of friends, let's keep it that way! Ute, Gina and Magali, our dinners are a blessing in the demanding everyday life. Ellis, Anita, and all others, we do our best every Friday, don't we?

Of course, my very fine 'paramifen' Tjallie and Tom. Thank you for standing by me in the planning for the event and on the day of my defense.

The last few years have been very busy. There have been a lot of things that have distracted me from working harder on this thesis, and this thesis has distracted me from working harder on other important things in my life: raising two small children and a number of teenagers; buying and renovating a house; trying to sell the old one; flamenco dancing ... the list could be made longer.

Of course, with two small children circulating around your legs, holding on to your skirt, I am more than grateful for all those helping out: Mor och Far, I am so glad that you are willing to travel such a distance every now and then, for us and for the children. Vera en Pierre, I am very thankful for the warmth that you direct towards us and "de kleintjes".

My lovely, heartwarming children: Hugo, Aat and Elsa. I cannot imagine how dull life would be without you! Olga, Oskar and Tom and Colinda, you are always there helping out and supporting in so many ways. I am so very lucky to have such wonderful children and stepchildren; you are all very precious to me!

Dearest Paulus, you are not on the official list of 'co-promotors', but you have been one in very many aspects. You read (and improved) almost all my papers in their various draft versions and you have encouraged me to do this all the time. You even took the time to make the lay-out of the book. It has not always been easy, but those wonderful, happy moments in-between and still to come make it all worthwhile.

Zeist, February 2011

Curriculum Vitae

Anna Lugnér was born in Malmö, Sweden on 20th February 1968. She grew up in Lund where she graduated from the upper high school Katedralskolan in 1986 with a diploma in natural sciences. Her academic education started at Lund Technical University in 1987, but she soon switched to political sciences at Lund University. In 1992 she received her bachelor's diploma in economics and advanced statistics. The same year she began her career at the Swedish Institute for Health Economics (IHE), where she worked for nearly 11 years. During that time, in January 2003, she received her diploma Licentiate of Philosophy in Economics at Lund University. Later that year she moved to the Netherlands. Since 2005 she is working at the National Institute for Public Health and the Environment (RIVM), Centre for Infectious Disease Control, Epidemiology and Surveillance Unit.

She is married to Paul and has three children: Hugo (1996), Aat (2005) and Elsa (2007), and three step children: Tom (1987), Oskar (1989) and Olga (1993).